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RELATION OF THE ADRENAL CORTEX TO RHEUMATIC DISEASE

A REVIEW OF SOME RECENT INVESTIGATIONS

BY

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For years the literature has contained reports which have suggested that certain rheumatic diseases may be related, in some vague way, to the function of the endocrine glands. Some writers envisaged the possibility of an " endocrine rheumatism " and some even considered, along with other aetiological theories, that rheumatoid arthritis might be elicited through an obscure hormonal imbalance. Such ideas were ill-defined and lacked both experimental and direct clinical support. Recently, however, Hench, Kendall, Slocumb, and Polley, and subsequently others, have demonstrated that an adrenal cortical hormone (cortisone) and a pituitary adrenocorticotrophic hormone (ACTH) exert strikingly beneficial effects on a variety of rheumatic diseases. These observations now serve as strong evidence to link the pathogenesis of certain rheumatic diseases with the function of the endocrine glands, especially the adrenal cortex.

APPLICATION OF ADRENAL CORTICAL FUNCTION TO THE RHEUMATIC DISEASES

The reasoning which eventually led to the discovery that certain hormonal compounds exert powerful anti-rheumatic action was presented in detail by Hench[1].* It has long been known that rheumatoid arthritis is capable of undergoing spontaneous regression and that the course of the disease may be punctuated by spontaneous remissions, partial or complete, temporary or permanent. The disease, therefore, has the inherent capacity of spontaneous reversibility although the potentiality often remains dormant[1]. Certain procedures, heretofore apparently unrelated in their mode of action, are known to stimulate, though feebly, this potential reversibility and thereby to induce temporary amelioration of the disease. Such procedures include febrile reactions from foreign proteins, starvation, surgery, and surgical anaesthesias. More potent and more regular antagonists of rheumatoid arthritis are pregnancy, and jaundice from biliary obstruction or hepatitis[2, 3, 4, 5, 6, 7]. Although the possible mechanism of

* As this article presents an exceptional number of references, we have departed from the usual practice in this Journal. The references will be found in numerical order corresponding to the notes in the text. All titles of articles are given in full.

relief from these various procedures and states appeared diverse and unrelated, Hench speculated that a common *modus operandi* might exist. Further, he was unable to harmonize the microbic theory of aetiology with the powerful ameliorative influence of jaundice and pregnancy, states which are not known to influence favourably the course of proved bacterial or virus infections. If the agent producing articular relief in jaundice were closely related to or identical with the agent responsible for relief in pregnancy, Hench reasoned that the responsible substance must be common to both sexes and was not a unisexual factor. He conjectured that a bisexual hormone, possibly an adrenocortical hormone, might be involved in the curious anti-rheumatic effect of pregnancy.

In September, 1948, Hench, Kendall, Slocumb, and Polley[8] administered the adrenal cortical hormone, cortisone (Compound E), to a patient with severe rheumatoid arthritis; striking and rapid improvement in the clinical and laboratory features of the disease resulted. In April, 1949, these investigators reported dramatically favourable effects on severe or moderately severe rheumatoid arthritis from cortisone in fourteen patients and from adrenocorticotrophic hormone (ACTH) in two patients. Subsequently it has been found that cortisone and/or ACTH exert a beneficial influence on other rheumatic diseases, including to date acute rheumatic fever, rheumatoid (ankylosing) spondylitis, disseminated lupus erythematosus, periarteritis nodosa, psoriatic arthritis, dermatomyositis, and gout.

Historical Notes on Cortisone and Early Experimental Studies

In 1936 Kendall and his co-workers[9] reported the isolation of nine separate, but closely related, steroid hormones from extracts of the adrenal cortex. Among these was a compound, later known as Kendall's Compound E, of which the chemical formula was found to be $C_{21}H_{28}O_5$[10, 11]. In the same year an identical substance was also isolated by Wintersteiner and Pfiffner (their Compound F)[12, 13], and by Reichstein (his Compound F_a)[14]. In 1938 Mason, Hoehn, and Kendall determined the chemical structure of Compound E to be 17-hydroxy-11-dehydrocorticosterone[15]. In 1949 Compound E was renamed cortisone.

The known hormones of the adrenal cortex may be classified broadly according to their principal functions as follows: (1) electrolyte regulating steroids (mineralocorticoids); (2) carbohydrate regulating steroids (gluco-corticoids or glycogenic corticoids); (3) sex-like steroids (principally androgenic steroids). Cortisone belongs to the group of carbohydrate-regulating hormones, along with Compounds A (11-dehydro-corticosterone), B (corticosterone), and F (17-hydroxy-corticosterone). These substances have an oxygen atom attached to the eleventh carbon position in the phenanthrene ring. More specifically, cortisone and Compound F have oxygen atoms at both the eleventh and seventeenth carbon positions, and hence are known as 11-17 oxysteroids; these two substances are the most active of the carbohydrate regulating hormones.

After more than eight years of research, in co-operation with Kendall and co-workers at the Mayo Clinic, partial synthesis of cortisone from a bile acid

(desoxycholic acid) was accomplished in 1946 by L. H. Sarett at the Merck Laboratories[16]. Continued research resulted in improvements in the synthesis, and in 1948 sufficient material was accumulated to allow very limited evaluation of the compound. Cortisone is now being prepared and used in the form of its acetate ester (cortisone acetate: 17-hydroxy-11-dehydrocorticosterone-21-acetate). The product is still scarce, but its physiologic properties and clinical applications are being determined at an accelerated rate by a number of investigators.

Prior to its synthetic production, only minute quantities of cortisone were available for research purposes. The scarcity of the naturally-occurring hormone may be appreciated by the fact that one-half ton of beef adrenal gland tissue yielded, on extraction, only 340 mg. of cortisone[17]. Yet, in spite of its scarcity, certain important facts regarding its physiologic activity were determined prior to 1948, some of which will be mentioned herein.

Early investigations indicated that cortisone and other adrenal cortical steroids having an oxygen atom at the eleventh carbon position exerted a definite influence on carbohydrate metabolism[18, 17, 19]. Cortisone given to normal rats (forced fed with a high carbohydrate diet) produced transient hyperglycaemia and glycosuria[20]. When administered to partially depancreatized animals with intact adrenal glands, it intensified the glycosuria, and when given to partially depancreatized-adrenalectomized animals, glycosuria reappeared[21, 17, 23]. Because of concomitant increases in excretions of nitrogen and potassium, it was reasoned that cortisone (and other 11-oxysteroids) stimulated gluconeogenesis by manufacturing glucose at the expense of tissue proteins[21]. Later studies, however, suggested that gluconeogenesis may not be accomplished by catabolism of body protein, but by a process of blocking protein synthesis whereby amino acid radicals are diverted to pyruvic acid and glucose (anti-anabolic effect)[23, 24, 25]. When adrenalectomized[26, 27] or hypophysectomized[28] animals were subjected to phlorhizin and then injected with cortisone an increased excretion of glucose and nitrogen occurred, indicating that the hormone is capable of replacing the gluconeogenic function of the adrenal gland. The hormone was found to counteract effectively the hypoglycaemic effect of insulin[17, 29, 33] and to promote the deposition of glycogen in the liver and muscles[30, 18, 31, 32]. In patients with Addison's disease whose electrolyte balance was maintained with desoxycorticosterone, the administration of cortisone corrected the abnormal carbohydrate metabolism; the fasting blood sugar level was raised, the respiratory quotient decreased, and the threshold for hypoglycaemic reactions increased[34]. In subjects with coexisting Addison's disease and diabetes mellitus, the diabetes was intensified when cortisone was administered in daily doses of 8 to 20 mg.[35]

Cortisone given to human subjects over long periods has little overall effect on electrolyte metabolism[36, 37, 38]. At first there may be a negative sodium balance, but later the balance becomes levelled off. According to Thorn, cortisone and its related 11-oxysteroids exert a weak sodium-retaining effect, about one-thirtieth of that produced by desoxycorticosterone. However, under certain conditions, as in the presence of excessive sodium retention induced by desoxycorticosterone,

cortisone (also Compound F) may act in competition and cause increased sodium excretion[23]. Cortisone was found to cause increased excretion of potassium and phosphorus in partially depancreatized-adrenalectomized rats[25]. Its administration to normal subjects and in patients with gout produced increased renal clearance of uric acid resulting in the excretion of large quantities of urates[23]. Young rats receiving the hormone exhibited a decrease in the phosphatase activity of the bony epiphyses[39].

Cortisone given to young rats suppressed their growth and development, and in both sexes caused marked atrophy of the adrenal and thymus glands[40]. Similar atrophy was noted in the spleen and lymph nodes[24, 41] which suggested that the hormone might have a regressive effect on certain types of lymphatic tumour[42]. Subsequently it was found that adrenalectomized rats showed an augmented susceptibility to transplanted lymphatic leukaemia, indicating that adrenal secretions might have an inhibitory effect upon the development of this disease[43]. Heilman and Kendall demonstrated that transplants of a highly malignant mouse tumour (diagnosed as lymphosarcoma) which was transmissible to mice in almost 100 per cent. of instances failed to grow if the recipients received cortisone[42]. Pronounced regression of these tumours, even though well developed, occurred with administration of the hormone. A lysis of fixed lymphoidal tissue, a transient decrease in circulating lymphocytes, and a marked decrease of circulating eosinophils from the blood have been noted during short-period administration of cortisone[23].

Cortisone and other 11-oxysteroids have the capacity of increasing muscle strength and efficiency in adrenalectomized animals[22, 44, 45]; this effect is not observed in animals with intact adrenal glands. Physiologic resistance to stress and shock is greatly enhanced in adrenalectomized animals when cortisone is administered. Not more than 0·03 mg. of the hormone is required to protect adrenalectomized rats against 25 minimal lethal doses of typhoid vaccine, and the substance is highly effective in protecting such animals against low temperatures[39].

Historical Notes on ACTH and Early Experimental Data

Accumulated evidence indicates that the major regulator of adrenal cortical function is the anterior pituitary gland, and that this regulation is achieved through the secretion of adrenocorticotrophic hormone (ACTH). In 1930 it was shown that ablation of the anterior pituitary gland in rats resulted in adrenal cortical atrophy, and that this atrophy could be prevented or corrected by daily homoeotransplants of anterior pituitary substance[46]. In 1933 Collip[47] isolated an impure "adrenotropic hormone" which contained adrenocorticotrophic principle in potent amounts. In 1943 a pure form of the hormone, unadulterated by other secretions in the gland, was isolated by Li and his collaborators[48] from sheep pituitary glands, and by Sayers and co-workers[49] from swine pituitaries. The hormone so derived was a complex protein substance with a molecular weight of nearly 20,000 and an isoelectric point of approximately 4·7[48]. More recently

it has been demonstrated that the active adrenocorticotrophic principle is contained in a peptide fraction of ACTH[50].

The major physiologic effects of ACTH are dependent on stimulation of the adrenal cortices to produce steroid hormones. Its administration to animals and humans with intact adrenal glands results in increased secretion of glucocorticoids, some of which are closely allied to cortisone, but also to a lesser degree in increased secretion of other cortical steroids, such as those which influence electrolyte metabolism and androgenic function. Thus, in animals[51, 52, 53, 54, 55, 56, 33] and human subjects[57, 58, 59, 38, 23], the administration of ACTH produces in general the following results: it affects carbohydrate and protein metabolism (inducing hyperglycaemia, glycosuria, and negative nitrogen balance); it alters electrolyte metabolism (inducing increased excretion of potassium and decreased excretion of sodium); it inhibits growth of young animals and produces thymus atrophy; it reduces the alkaline phosphatase content of plasma; it promotes haematologic changes which include falls in total eosinophil and lymphocyte counts, increase in circulating neutrophils, and atrophy of lymph nodes; it causes prompt and pronounced increased excretion of corticosteroids and 17-ketosteroids; it enhances the excretion of uric acid; and it augments anti-hyaluronidase activity. In patients with Addison's disease or in adrenalectomized animals, these effects are not produced.

With administration of ACTH to animals, adrenal cortical hypertrophy may result[60], and the cholesterol and ascorbic acid contents of the gland are quickly reduced[61, 62, 63, 64]. A single dose of ACTH may result, within 3 hours, in a 50 per cent. decrease in the gland's cholesterol concentration, and during the period of cholesterol depletion evidences of increased cortical hormone activity are observed. This suggests, but does not prove, that cholesterol may be utilized in the formation of steroid hormones[65]. The relationship between ascorbic acid and the cortical steroids is not established, but the gland's sensitive response to ACTH is now used as a means of bio-assaying the potency of ACTH.

Experimental Data Implicating the Adrenal Cortex in the Pathogenesis of Rheumatic Disease

That the function of the adrenal cortex may be involved in the pathogenesis of certain rheumatic diseases was suggested by Selye and his co-workers in 1944. Rats with intact adrenal glands, when treated with large doses of desoxycorticosterone, occasionally developed joint lesions which were similar histologically to the articular lesions of rheumatic fever[66]. The arthritis was transient and tended to disappear in a few weeks in spite of continued administration of the hormone. While the arthritis was produced in only a small percentage of the animals, other changes of a " rheumatic type ", such as arteritis simulating periarteritis nodosa, myocarditis with Aschoff body formation, and encephalitis accompanied by choreiform twitches, occurred quite regularly. In adrenalectomized rats, the articular manifestations developed more frequently and extra-articular lesions were

more pronounced[66, 67, 68]. Thyroidectomy and exposure to cold also increased the frequency by which experimental arthritis could be provoked with desoxycorticosterone, but to a lesser degree. Selye suggested that adrenalectomy may sensitize the animal to the toxic effects of desoxycorticosterone by removing the endogenous source of gluco-corticoids which may inhibit or oppose the action of such mineralo-corticoids as desoxycorticosterone. Similar lesions in the joints and heart were produced in rats with intact adrenal glands by injecting a crude lyophilized anterior pituitary preparation[69]. Because adrenalectomy prevented these changes, the effects of the preparation were believed to be mediated through the adrenal cortex, possibly by causing an excessive discharge of mineralo-corticoids.

These and other observations led Selye to include rheumatic diseases (rheumatic fever, rheumatoid arthritis, so-called collagen diseases, and gout) among those maladies interpreted by him as " diseases of adaptation "[70, 69, 66, 71]. According to this theory, the organism normally responds to a variety of stress-provoking agents (emotional tension, infections, intoxications, exposure to cold, etc.) with an increased and balanced corticoid hormone production—a useful " adaptation reaction " which increases resistance in general. Under abnormal conditions, however, there may be an imbalanced elaboration of adrenal cortical hormones with gluco-corticoid production failing to keep pace with the excess out-pouring of mineralo-corticoids[72]. The reasoning leading to this concept was based on the apparent opposing actions of mineralo-corticoid and gluco-corticoid hormones: pre-treatment of animals with desoxycorticosterone tends to cause thymus hypertrophy[73, 74], hypoglycaemic response to stress-producing agents,[75] and aggravation of shock from surgical trauma, while pre-treatment with gluco-corticoids produces opposite effects[69, 76, 77].

In November, 1949, Selye[72] reported observations on the influence of certain anterior pituitary and adrenal cortical hormones on the production and prevention of experimental arthritis. By the local injection of dilute solutions of formaldehyde into the tissues near a joint, acute arthritis and periarthritis were produced. When large or repeated doses of formaldehyde were injected, chronic arthritis and periarthritis developed. These were self-maintaining proliferative reactions that continued for weeks after stopping the irritant. Microscopically the lesions resembled those found in the " chronic stage of rheumatoid arthritis ". This experimental arthritis was intensified if the rats were given either desoxycorticosterone or crude lyophilized anterior pituitary extract for several days before formaldehyde was injected. Conversely, pre-treatment with either cortisone or ACTH almost completely inhibited the development of " formalin arthritis ". Furthermore, experimentally produced alarm reactions (forced exercise, exposure to cold, spinal cord transection, starvation) inhibited the development of articular reactions from formaldehyde. The preventive effect of severe stress was interpreted as due to increased endogenous secretion of ACTH and hence of gluco-corticoids. Adrenalectomized animals subjected to similar stresses were not protected from " formalin arthritis ".

Deductions were drawn that the inhibitory actions of ACTH, cortisone, and the

alarm reaction on " formalin arthritis " were due to the direct effect of cortisone-like gluco-corticoids upon the injured tissues. Although the mechanism is not known, Selye suggested that it may be related to the anti-hyaluronidase effect of gluco-corticoids or to their anti-histaminic action. Selye cautioned that the anti-arthritic effects of ACTH and cortisone are not specific reactions directed against a hypothetical pathogen, but rather a non-specific effect.

EFFECTS OF CORTISONE AND ACTH ON CERTAIN RHEUMATIC DISEASES

From available information it is estimated that in America up to January 1, 1950, cortisone has been studied in about 160 patients with rheumatic disease, and ACTH in about 175 patients[78]. The majority of these patients have had rheumatoid arthritis. Clinical data from these studies are just beginning to appear in the literature, and hence much of the information included herein is based on reports yet to be published.

Rheumatoid Arthritis

Anti-rheumatic Effects of Cortisone.—Hench, Kendall, Slocumb, and Polley first reported the effects of cortisone on fourteen patients with severe, or moderately severe, rheumatoid arthritis[8]. The duration of the disease in their patients varied from four and a half months to five years, and the erythrocyte sedimentation rates ranged from 108 to 62 mm. in one hour (Westergren method). In nine of the fourteen patients cortisone was given for short periods ranging from 8 to 61 days. Five of the fourteen patients received the compound either continuously or intermittently for periods of 2 to 4 months. In their earlier cases doses of 100 mg. of cortisone were given intramuscularly each day; later 300 mg. were administered on the first day and 100 mg. daily thereafter. All analgesic agents, physical therapy, or other remedies were stopped several days or weeks prior to administration. In each case a prompt and striking improvement in the musculo-skeletal, constitutional, and laboratory manifestations of the disease resulted, and was maintained during the period of administration.

The dramatic response of rheumatoid arthritis to cortisone has been confirmed by Freyberg, Bauer, Holbrook, Rosenberg, and Boland[79]. The experiences of these investigators have been practically uniform and each has observed that the disease in its various manifestations is quickly and greatly improved with administration of the hormone. Boland and Headley[80] reported clinical observations in eight patients. Five of the eight patients had severe rheumatoid arthritis and were given large doses for short periods (total of 1 g. in divided doses for 8 days). The immediate results were decidedly pronounced improvement in three, pronounced improvement in one, and moderate improvement in one. Three additional patients with less severe rheumatoid arthritis (two with moderate and one with mild disease) were given smaller doses of the drug for longer periods; with daily doses of 50 mg. the symptoms and objective findings were adequately, but not completely, controlled.

A fairly definite pattern of improvement is noted with cortisone administration[8, 80, 81, 78]. Within a few days (or hours in some cases) there is a marked reduction of stiffness of muscles and joints, lessening of articular aching, tenderness, and pain on motion, and a significant improvement of articular and muscular function.

Usually the first symptoms to subside are muscular and articular stiffness and rest pain. Within 1 to 4 days the patients may have no further desire for acetylsalicylic acid or other analgesics. Next in order of improvement are lessening of joint pain on motion, increased motion, and decreased tenderness of the joints. Reductions in articular swellings are usually slower in appearing and may be not complete, but sometimes swellings and effusions recede rapidly and completely. Mild flexion deformities may be corrected within 7 to 10 days. Muscle strength and joint function may return to a remarkable degree within a few days, despite advanced muscle atrophy and previously restricted joint motion. In early and less severe cases, complete remissions may occur with disappearance of all abnormal physical signs; in cases of longer standing, some articular swelling and slight effusion, together with some tenderness, may persist even with the use of relatively large doses of the hormone. Destructive changes in the cartilage and bone, ankyloses, and ligamentous calcification remain unchanged. Other non-articular features, such as subcutaneous nodules, bursitis, and tenovaginitis, improve or disappear along with the improvement in the joints.

Anti-rheumatic Effects of ACTH.—Hench, Kendall, Slocumb, and Polley[8] gave ACTH in doses of 100 mg. daily for a period of 12 days to two patients with severe rheumatoid arthritis. Marked clinical improvement, essentially similar qualitatively to that resulting from the use of cortisone, occurred. Striking reductions in stiffness, pain, articular tenderness, and constitutional symptoms were noted within a few days. Side effects, such as a sense of exhaustion, transient gas pains, heaviness in the chest, and moderate elevation (20 to 30 mm.) of blood pressure, were observed. As with cortisone, the beneficial effects were temporary, and both clinical and laboratory manifestations of the disease promptly reverted to their original intensities after withdrawal of the hormone.

The observations made by Hench and his colleagues have been confirmed without exception by others[82, 83, 23, 84, 85, 78, 81, 86, 87, 88]. Thorn and others[23] treated ten rheumatoid arthritis patients with ACTH in doses of 40 mg. daily for periods ranging from 2 to 14 days. Nine of the ten cases improved promptly and significantly, improvement usually beginning within 12 to 24 hours after the initial injection. Sustained falls in the levels of circulating eosinophils, retention of sodium, and marked increases in 17-ketosteroid excretion occurred which served as evidence for adrenal cortical stimulation. The one patient who failed to improve received ACTH for only 48 hours; the eosinophil count did not fall but there was increased 17-ketosteroid excretion.

Remissions were obtained in each of nine patients with rheumatoid arthritis observed by Rosenberg[81]; effective doses ranged between 40 and 100 mg. daily.

Similar results have been observed by Holbrook[84] in 34 patients, and by Ragan, Grokoest, and Boots[87] in eight patients; the latter investigators were able to maintain good results with small daily doses (20 to 30 mg.) in two patients. Several of Holbrook's patients treated with daily doses of 40 mg. for 10 to 20 days retained 75 per cent. of the initial improvement for longer than 6 months. In general, those patients with less severe disease experienced longer periods of improvement after the hormone was discontinued.

Effects of Cortisone and ACTH on Constitutional Symptoms.—A striking sense of well-being is exhibited by most patients early in the period of cortisone or ACTH administration[8, 81, 78, 38]; the degree of mental stimulation varies somewhat with the size of the daily dose given[80]. Some patients, initially depressed and pessimistic, become frankly euphoric. In some the state of euphoria induced seems greater than would be expected from improvement in their physical condition and relief from pain. Other effects noted include loss of "toxic feeling", increased general strength and endurance, and increase in libido in some males. Febrile cases may become afebrile within 24 to 72 hours and remain so during the period of administration. Appetites usually improve rapidly with corresponding increases in food consumption and body weight. Hench and co-workers[8] noted weight gains in their patients as follows: 21·5 lb. in 10 weeks; 17·5 lb. in 2 months; 19 lb. in 40 days; 15 lb. in 27 days; 7·5 lb. in 26 days.

Effects of Cortisone and ACTH on Usual Laboratory Tests

Erythrocyte sedimentation rates.—Significant decreases in the erythrocyte sedimentation rate occur, usually within a few days after cortisone administration is started; in some patients the decreases occur promptly and rapidly, but in others more slowly. With cortisone in daily doses of 100 mg., the decreases usually continued at the rate of 2 to 4 mm. per day, but in some the correction was more rapid, proceeding with a daily average of 4 to 7 mm.; often rates become normal within 10 to 35 days[8]. With short-term administration of cortisone, decreases in rates varying from 15 to 75 mm. in a period of 8 days may be noted[80]. Even more prompt and more steady decreases result from the administration of large doses of ACTH[8].

Erythrocyte count and haemoglobin determinations.—When anaemia is present, erythrocyte counts may increase by 500,000 to 1,000,000 cells per c.mm., and haemoglobin determinations may increase by 1·4 to 2·0 g. per 100 cc. within a few weeks[8]. Even with short-term administration, marked improvement in the erythrocyte count and haemoglobin may be noted[80]. Treatment with ACTH results in similar corrections of anaemia.

Leukocyte counts.—Small, but significant, increases in the total number of circulating leukocytes have been noted during protracted administration of cortisone, but no significant changes in the number of lymphocytes or eosinophils occurred during or after administration of the hormone[38]. Short-term administration may cause significant decreases in lymphocytes and eosinophils[23]. When ACTH

was given in doses of 100 mg. daily, complete or almost complete disappearance of circulating eosinophils occurred[23, 89].

Articular biopsies.—When these were performed after several weeks of cortisone administration, definite evidences of healing were noted, but the synovial tissues were still not normal; microscopic findings included disappearance of lymphocytic reaction, improvement in the appearance of collagen, and the presence of many fibroblasts[8].

Electrocardiograms.—Except for slowing of the heart rate, no significant changes have been noted as the result of cortisone administration[80].

Electroencephalograms.—Changes in the electroencephalographic pattern have been observed with both cortisone and ACTH administration[80, 87]; full significance of these changes has not yet been reported.

Metabolic and Immunological Effects of Cortisone and ACTH.—Sprague and collaborators[38] conducted detailed metabolic studies on patients treated primarily for rheumatoid arthritis with cortisone and ACTH, five of whom were confined to a special metabolic unit for various balance studies. Similar investigations were reported by Ragan and associates[87] on patients receiving ACTH.

Corticosteroid excretion[38, 8].—Urinary concentrations of corticosteroids were increased initially when large doses (100 to 200 mg.) of cortisone were given. With continued administration of 100 mg. daily, the amount excreted remained elevated or declined toward control values. ACTH promoted pronounced corticosteroid excretion. Thirty to 50 per cent. of the total amount excreted consisted of Compound F (17-hydroxycorticosterone) indicating that ACTH stimulates the adrenal cortex to form Compound F rather than cortisone.

17-ketosteroid excretion[38, 8].—Administration of cortisone was followed by a prompt and striking fall in urinary 17-ketosteroid values. This suggested that the hormone depressed some functions of the adrenal cortex. Conversely, ACTH caused a prompt and pronounced increase in the excretion of 17-ketosteroids.

Plasma electrolytes[38, 87].—Cortisone in doses of 100 mg. daily for 12 to 14 days induced minimal alterations or no changes in the balances for nitrogen, calcium, phosphorus, sodium, potassium, and chloride, and in the concentrations of electrolytes in the extra-cellular fluid as measured in blood plasma. Cortisone in doses of 200 mg. daily for 12 to 18 days regularly induced a negative balance for nitrogen and potassium. The effects of such large doses on excretion of sodium and chloride were variable; the most common were retention of these ions at first, followed later by increased excretion. ACTH in doses of 100 mg. daily for 12 days induced a negative balance for nitrogen and potassium. Initially a marked retention of sodium and chloride occurred, then later these ions were excreted in increased amounts; some lowering of the serum sodium occurred concomitantly.

Urinary total nitrogen[38, 87].—Augmentation of nitrogen excretion was slight or absent when the dose of cortisone was 100 mg. daily, and pronounced when the dose was 200 mg. daily. A negative nitrogen balance occurred during ACTH

administration in large doses (100 mg.), but nitrogen excretion sometimes fell to control levels when the daily dose was lowered.

Uric acid in serum and urine[38, 87].—Uric acid excretion was only slightly increased with the administration of 100 mg. of cortisone daily. The excretion was moderately increased with ACTH in daily doses of 100 mg. Significant decreases in serum uric acid occurred most commonly with ACTH or cortisone administration when the serum uric acid levels were initially in the upper normal range or above normal.

Creatine and creatinine nitrogen in urine[38, 87].—Marked increased creatinuria was found during the early phase of cortisone and ACTH administration. The increased excretion may or may not continue during the period of treatment. Urinary creatinine nitrogen exhibited no changes which could be attributed to ACTH or cortisone.

Carbohydrate tolerance[80, 38, 87].—Slight inconstant increases in the fasting blood sugar were observed in some cases during administration of cortisone or ACTH, but the values did not exceed normal range. Carbohydrate tolerance tests were not conspicuously altered although slightly decreased tolerances were noted in a few cases during the period of cortisone administration.

Glutathione in the blood[78].—During the administration of cortisone or ACTH there was no consistent pattern of change in the glutathione of whole blood or of erythrocytes.

Glucuronic acid and gentisic acid excretion[87].—The excretion of neither substance increased during ACTH administration.

Serum proteins[38, 87, 8].—The effect of cortisone and ACTH was to increase serum albumin and decrease serum globulin if the pre-treatment values of these substances were abnormal.

Basal metabolism and respiratory quotient[38].—When the basal metabolism was raised (because of the rheumatoid arthritis and not hyperthyroidism), it became normalized with the administration of either cortisone or ACTH. This resulted apparently from improvement in the rheumatic state. Consistent changes in the respiratory quotient were not observed.

Sensitized sheep cell agglutination[87].—Only one of eight patients showed a fall from the rheumatoid range to the normal range during treatment with ACTH; the one exception had an initially weak positive titre.

Group A streptococcus agglutination[87].—This reaction remained positive in seven of eight patients treated with ACTH; in one instance a positive agglutination changed to a doubtful reaction.

Serum cholesterol[87].—Of seven patients with rheumatoid arthritis, four showed a rise in serum cholesterol, both free and esterified, during ACTH treatment.

Blood sludging[90].—When clinical improvement was greatest during cortisone administration, the degree of blood sludging was significantly decreased in several cases.

Dosage and Schedule of Administration of Cortisone and ACTH.—To accomplish remissions in adults with severe, or moderately severe, rheumatoid arthritis, Hench,

Kendall, Slocumb, and Polley[8] found that approximately 100 mg. of cortisone daily were required. In their later cases they adhered to a schedule consisting of 300 mg. given on the first day and 100 mg. daily thereafter. In severe cases smaller doses of 25 to 50 mg. were inadequate or ineffective. In moderate and mild cases Boland and Headley[80, 91] found that doses averaging 50 mg. daily were sufficient to control the clinical manifestations and cause the erythrocyte sedimentation rate to revert to normal; 100 mg. doses given every other day were as effective as 50 mg. doses given daily. In some severe cases, initially brought under control with large doses of cortisone, improvement has been maintained by smaller doses of 50 to 75 mg. given daily, or 100 to 150 mg. given every other day[91]. Freyberg[78] had continued good results in several cases with doses of 100 mg. three times a week. Hench[92] reported that intermittent treatment (periods of daily injection separated by periods of several weeks' rest from treatment) has given good results in several patients, with less relapse after each period of injections.

With ACTH remissions may be accomplished with daily doses ranging from 20 to 100 mg.[23, 87, 81, 84]. More effective stimulation of the adrenal cortices appears to be accomplished by injections of hormone in small doses four times daily, than by one large dose per day[78]. After 25 mg. of ACTH have been given four times on the first day, doses of 10 or 15 mg. four times daily usually maintain good remissions, even in severe cases. Ragan and co-workers[87] held two patients under satisfactory control with doses of 10 or 15 mg. given twice daily. Unfortunately the doses of ACTH employed must vary from time to time according to the potency of individual batches; the milligram dosage of different lots cannot be compared and doses must refer to a biologic standard.

Much more experience is needed before the question of optimal maintenance dosage can be settled. It appears that the dose necessary to produce adequate suppression depends upon a number of variable factors, but particularly on the severity and current activity of the disease process. Because of potential endocrine complications arising from large doses given for prolonged periods, it may be more prudent at times to maintain good but incomplete results with small doses than to strive for complete results with large doses[78]. In the case of cortisone this may be closer to what Hench has referred to as " co-operating with, rather than taking over completely " the function of the adrenal cortex[92].

Course after Discontinuance of Cortisone and ACTH.—Sustained improvement appears to be dependent upon continued administration, and cessation of the hormones is usually followed by prompt, or fairly prompt, relapse of the disease. In eight out of nine cases reported by Hench, Kendall, Slocumb, and Polley[8], in which cortisone was discontinued after short-term administration, the symptoms and signs began to return within 2 to 4 days after withdrawal of the compound; the return progressed slowly in six, but rapidly in two cases. The remaining one case retained most of the improvement 5 months after the drug was stopped. In seven of eight cases observed by Boland and Headley[80] relapse occurred on withdrawal of the medication, and within 4 weeks the clinical and laboratory manifestations returned

to their original intensities. One of their cases retained 75 per cent. of the initial improvement. As with cortisone, withdrawal of ACTH is usually followed by rapid return of symptoms[8, 87, 23, 81, 78, 84].

Signs of Hyperadrenalism from Cortisone and ACTH.—Objective clinical signs of hyperadrenalism have occurred in some cases when these hormones have been given for extended periods and in large doses; such signs disappeared when the administration was stopped. With smaller daily doses endocrine changes have not been reported. Because of the many physiologic alterations induced by both cortisone and ACTH, some of which do not have favourable therapeutic implications, signs of endocrine disturbance should be termed "signs of hyperadrenalism" or "other physiologic effects" rather than "toxic reactions"[38]; the latter term implies a clinically restricted appreciation of the biologic significance of these substances.

Rounding of the facial contour ("moon-like facies") is one of the earliest signs of hormonal excess; this may or may not be associated with some fuzzy hair growth[78, 84, 38]. Disturbances in the menstrual cycle, usually in the form of irregular menses or amenorrhoea, may occur with prolonged administration. Transient oedema, usually pretibial, has occurred in a few cases; this has disappeared spontaneously, or when the dose of the drug has been reduced, or when saline diuretics have been administered[8, 81, 78]. One patient exhibited numerous subcutaneous ecchymoses about the thighs and buttocks during cortisone administration[81]. Another patient, a 29-year-old female who was given large doses of cortisone daily for 6 months, developed definite signs of hyperadrenalism characterized by mild acne and hirsutism, rounding of the facial contour, amenorrhoea, and mental depression. The manifestations suggested a mild Cushing's syndrome, but were reversible and disappeared when cortisone was discontinued[93]. In a patient with co-existing diabetes mellitus and rheumatoid arthritis, the diabetes was temporarily intensified[80]. During cortisone administration the daily insulin requirement increased from 10 units to between 30 and 50 units while the patient was on a constant measured diet; 3 days after withdrawal the insulin requirement reverted to the pre-cortisone amount of 10 units. Freyberg[78] has encountered no serious complications in a series of seventeen patients treated with cortisone; treatment was continued in some for as long as 160 days. There appears to be a decidedly greater chance for complications in females than in males, especially during their pre-menopausal years, because of the more complex gonadal functions.

Juvenile Rheumatoid Arthritis (Still's Disease)

Juvenile rheumatoid arthritis has responded in the same way as the adult form to cortisone and ACTH[78, 84, 86, 81]. The details of two cases of juvenile rheumatoid arthritis were reported by Elkinton and collaborators[86]. One, a 5-year-old boy, was treated with 25 mg. of ACTH daily for 7 days; within 12 hours he became

afebrile and within 48 hours most of the painful joint swellings had subsided. The other, a 9-year-old girl, was given ACTH intermittently and in varying doses over a period of 152 days. Dramatic clinical improvement resulted during each period of administration, but with daily doses of 50 to 60 mg., signs of hyperadrenalism ensued (acne, oily hair, mild hirsutism, and moon-shaped or Cushing's facies). In Freyberg's experience adequate dosage of these hormones in children depends more on the severity of the disease than on body size[78]. For good antirheumatic effects as much may be needed as in an adult, but the metabolic and endocrine complications may be greater in the child because of the larger ratio between hormone dose and body size.

Rheumatoid (Ankylosing) Spondylitis

Results similar to those obtained in peripheral rheumatoid arthritis have been produced by cortisone or ACTH in cases of typical rheumatoid (ankylosing) spondylitis. Temporary remissions were provoked in each of six cases treated by Freyberg with cortisone[78]. Holbrook gave ACTH in doses of 40 mg. daily for 10 to 14 days to four spondylitic patients (three males and one female) and decided improvement occurred in each during the course of administration[84]. One patient retained 75 per cent. of the improvement for three months, whereas the remaining three patients experienced prompt exacerbations when the administration of hormone was stopped.

Rheumatoid Arthritis with Psoriasis and Psoriatic Arthritis

A few patients with rheumatoid arthritis and co-existing psoriasis have been given ACTH or cortisone; the articular response has not differed from that observed in uncomplicated rheumatoid arthritis, and in each instance there has been marked improvement or complete clearing of the skin lesions[94, 84, 81]. A patient with typical severe psoriatic arthritis and radiographic changes of psoriatic arthropathy was given cortisone in daily doses of 100 mg. for a prolonged period; marked subjective and objective improvement in the joint manifestations resulted together with improvement, but not disappearance of the psoriasis[91].

Acute Rheumatic Fever

Hench and others[36] administered cortisone to three adolescent patients with acute rheumatic fever; two were undergoing their first attack and the third was probably having a recurrence. For several days 200 mg. were given daily and then 100 mg. were given daily for a few days. In each patient there was rapid disappearance not only of fever, tachycardia, and polyarthritis, but also of sedimentation rate elevations and electrocardiographic abnormalities. Fever disappeared within one to four and a half days. The joints became symptom-free within 3 to 6 days except for mild metatarsal tenderness which persisted for 8 more days in one case.

Sedimentation rates were refractory for the first 2 to 5 days and then fell rapidly, decreases as great as 100 mm. being noted within periods of 10 to 14 days. Tachycardia disappeared within 3 to 5 days and prolonged P-R intervals in two patients were restored to normal within 7 and 8 days respectively. Weight gains, feeling of well-being, and loss of toxic symptoms were experienced by each patient. No definite evidences of toxicity were noted, but one patient developed mild rounding of the facial contour which subsided after cessation of the hormone. No definite conclusions were drawn as to the effects of cortisone in preventing or lessening chronic sequelae in the heart valves or myocardium. Hope was expressed, however, in view of the markedly beneficial effect of cortisone on skeletal muscles and fibrous tissues, that the compound will exert a similar sparing effect on the cardiac muscles and fibrous valves.

The same investigators[36] gave " small doses " of ACTH to a 14-year-old boy with rheumatic fever; fever subsided rapidly, the erythrocyte sedimentation rate fell and the articular manifestations disappeared within 4 days. Thorn and collaborators[23] treated three patients with doses of 40 mg. daily for periods ranging from 8 to 14 days; detailed results were not given but the response was said to be more striking than that obtained with ACTH in rheumatoid arthritis.

Periarteritis Nodosa

Ragan and associates[95] treated three cases of periarteritis nodosa with ACTH, and in each there was subsidence of the activity. Disappearance or marked improvement of such manifestations as purpuric rashes, pruritis, asthma, periarteritic nodules and eosinophilia resulted. In each instance the disease manifestations recurred when the hormone was discontinued.

Disseminated Lupus Erythematosus

Three patients with acute disseminated lupus erythematosus, observed by Thorn and associates[23], experienced marked clinical improvement during the administration of ACTH in daily doses of 40 mg. Two patients were treated with ACTH by Elkinton and others[86]. One patient given daily doses of 100 mg. became afebrile within 16 hours and the cutaneous lesions cleared within 14 days. The drug was then given in progressively smaller amounts and discontinued after 51 days. Remission remained " fairly complete " 60 days after stopping the hormone. The other patient had severe and apparently terminal disease with multiple visceral changes. Striking improvement, with fall in temperature, clearing of retinopathy, disappearance of pleural effusion, and diminution of the hepato-splenomegaly, resulted from the administration of 75 to 160 mg. of ACTH daily. At about the forty-fourth day of treatment, the patient apparently became refractory to the agent, and the manifestations returned. Despite doses of 200 mg. daily the patient died. In addition to advanced changes of disseminated lupus erythematosus, necropsy revealed normal-sized adrenal glands which were depleted of lipid.

Dermatomyositis

Elkinton and others[86] treated a severe case of dermatomyositis in a 5-year-old boy with three courses of ACTH. Following cessation of the first two courses, the disease relapsed, but after the third and more prolonged course the disease had remained in complete remission for 117 days (at the time of the report).

Gout

Recent studies have implicated the pituitary-adrenocortical mechanism in gout and gouty arthritis. Robinson and co-workers[96, 97] found that ACTH given to normal non-gouty subjects resulted in a prompt increase in urate excretion which persisted throughout the injection period and reached its peak on the ninth day; there was no accompanying decrease in the blood urate value as determined by the uricase method. A pronounced drop in urate excretion occurred on the first post-injection day, followed by unusually high values on the second and third post-injection days, after which values did not differ significantly from the pre-injection control period. Similar results were observed by Thorn and others[98], who could not account for the increase on the basis of accelerated renal excretion alone, and postulated that the hormone must also increase urate production in the normal subject. Administration of ACTH to a patient with latent pre-tophaceous gout and hyperuricaemia resulted in prompt increase in urinary excretion comparable in magnitude to that seen in normal subjects[98]. In contrast to normal subjects, however, there was a concomitant fall in blood urate levels which were less than 50 per cent. of the original value on the fourth day of hormone administration. Certain calculations suggested that ACTH caused increased production of urates as well as increased clearance by the kidney. The effects of colchicine and epinephrine were also studied on a gouty patient during an asymptomatic period; neither substance produced an effect on the urate levels; epinephrine caused the expected sharp drop in the eosinophil count, whereas colchicine had no such effect.

ACTH given during an acute attack of gouty arthritis will promptly produce relief in the acute joint manifestations[99, 100, 97, 101]. The attack may be suppressed for 24 hours or longer by a single dose of 50 mg. given within 8 hours of the onset. In most instances relief from all manifestations, except slight residual soreness, occurs within a few hours of administration. In some instances a second or third dose is required 6 to 12 hours later. However, the attack usually recurs in the same or other joints when ACTH is withdrawn. Colchicine given during, or immediately after, treatment of acute gouty arthritis with ACTH was found by some[100], but not by others[84], to prevent a renewal of the attack on ACTH withdrawal.

Robinson, Conn, Block, and Louis[96] and Hellman[99] gave ACTH to gouty patients during interval or latent periods between attacks, and then withdrew the hormone. On withdrawal the majority of patients given more than 100 mg. of ACTH during a 24-hour period developed an acute episode of gouty arthritis. The attack so provoked was relieved by further administration of ACTH, but again on withdrawal most patients developed another attack within a few days. This

phenomenon has been interpreted by Wolfson[100] as follows: ACTH withdrawal produces a lack of 11-oxysteroid which appears to precipitate acute gouty arthritis, whereas the induction of a state of 11-oxysteroid excess by administration of ACTH relieves the attack.

Administration of cortisone in large doses (200 to 300 mg.) produced prompt subsidence of objective and subjective manifestations in two cases with acute gouty arthritis studied by Boland and Headley[91]; relief occurred within 5 hours in one and within 18 hours in the other. As with ACTH, withdrawal resulted in an acute recurrence of the attacks. In one case the recurrent episode was again suppressed by a second injection of 300 mg. of cortisone and the attack was terminated without further recurrence by giving progressively smaller daily doses over a period of 8 days. They also observed a patient with tophaceous gout whose subacute articular manifestations involving several joints subsided completely in 20 days with the daily administration of 100 mg. of cortisone; concomitant diminution in size of subcutaneous tophi to 10 per cent. of their original dimensions was noted.

Wolfson and associates[102, 103] observed that the urinary output of 17-ketosteroids was uniformly greatly diminished in gouty patients both during acute attacks and during asymptomatic intervals. Such decreases were not found in patients with non-gouty hyperuricaemia. These findings suggested that in gout there may be either failure of both gonadal or adrenal androgen production or a more obscure disturbance in steroid metabolism. Being unable to explain the very low 17-ketosteroid output by other means, these investigators assumed that biologic androgen activity in gout is maintained by an abnormal androgen of adrenocortical origin which, when metabolized, makes no important contribution to urinary 17-ketosteroids.

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Ecorce Surrénale par Rapport à la Maladie Rhumatismale Revue de quelques Investigations Récentes

Résumé

1. Application de la fonction surrénale corticale aux maladies rhumatismales:
   (a) Notes historiques sur le cortisone et les premières études expérimentales. Composés E, F, et F_a. Classification des hormones connues de l'écorce surrénale. Effets du cortisone et de l'hormone adrénocorticotrophique (ACTH) sur animaux et sur hommes.
   (b) Données expérimentales impliquant l'écorce surrénale dans la pathogénie de la maladie rhumatismale.

2. Effets du cortisone et du ACTH sur certaines maladies rhumatismales:
   (a) Arthrite rhumatismale:
   Effets anti-rhumatiques du cortisone et du ACTH.
   Effets du cortisone et du ACTH sur les symptômes constitutionnels.
   Effets sur les épreuves de laboratoire (sédimentation globulaire, numération des érythrocytes et détermination de l'hémoglobine, numération des leucocytes, biopsies articulaires, électrocardiogrammes, électroencéphalogrammes).
   Effets métaboliques et immunologiques (excrétion corticostéroïde, excrétion des 17-cétostéroïdes, électrolytes du plasma, azote total urinaire, acide urique dans le sérum et dans l'urine, azote de la créatine et de la créatinine dans l'urine, tolérance des hydrates de carbone, glutathion dans le sang, excrétion de l'acide glucuronique et gentisique, protéines sériques, métabolisme de base et coefficient respiratoire, agglutination du sang de mouton sensibilisé, agglutination du streptocoque du groupe A, cholestérol sérique, " blood sludging ").
   Posologie et mode d'administration.
   Evolution après l'interruption du traitement.
   Signes objectifs de l'hyperactivité surrénale.
   (b) Arthrite rhumatismale juvénile (maladie de Still).
   (c) Spondylite ankylosante.
   (d) Arthrite rhumatismale avec psoriasis et arthrite psoriasique.
   (e) Rhumatismale articulaire aigu.
   (f) Périartérite noueuse.
   (g) Lupus érythémateux disséminé.
   (h) Dermatomyosite.
   (i) Goutte.

L'article est augmenté par une bibliographie épuisante de la littérature, mais beaucoup de renseignements, pas encore publiés, furent communiqués personnellement.

Corteza Suprarrenal con Relacion a la Enfermedad Reumática Revista de Algunas Investigaciones Recientes

RESUMEN

1. Aplicación de la función suprarrenal cortical a las enfermedades reumáticas:
   (a) Notas históricas sobre el cortisón y primeros estudios experimentales. Compuestos E, F, y F_a. Clasificación de las hormonas conocidas de la corteza suprarrenal. Efectos del cortisón y de la hormona adrenocorticotrófica (ACTH) sobre sujetos animales y humanos.
   (b) Datos experimentales implicando la corteza suprarrenal en la patogenesis de la enfermedad reumática.
2. Efectos del cortisón y de la ACTH sobre ciertas enfermedades reumáticas:
   (a) Artritis reumatoide:
   Efectos anti-reumáticos del cortisón y de la ACTH.
   Efectos del cortisón y de la ACTH sobre síntomas constitucionales.
   Efectos sobre pruebas de laboratorio (sedimentación globular, recuentos de eritrocitos y determinación de la hemoglobina, recuentos de leucocitos, biopsias articulares, electrocardiógramas, electroencefalógramas).
   Efectos metabólicos e inmunológicos (excreción corticoesteroide, excreción de los 17-cetoesteroides, electrolitos del plasma, nitrógeno urinario total, ácido úrico en el suero y en la orina, tolerancia de los hidratos de carbón, glutation en la sangre, excreción del ácido glucurónico y gentísico, proteinas séricas, metabolismo de base y el cociente respiratorio, aglutinación de la sangre sensibilizada de oveja, aglutinación del estreptococo del grupo A, colesterol sérico, " blood sludging ").
   Dosis y horario de administración.
   Evolución después de la interrupción del tratamiento.
   Indicios objetivos del hiperadrenalismo.
   (b) Artritis reumatoide juvenil (enfermedad de Still).
   (c) Espondilitis anquilosante.
   (d) Artritis reumatoide con psoriasis y artritis psoriática.
   (e) Reumatismo articular agudo.
   (f) Periarteritis nodosa.
   (g) Lupus eritematoso diseminado.
   (h) Dermatomiositis.
   (i) Gota.

El artículo está completado por una bibliografía minuciosa de la literatura, pero mucha información no publicada aún procede de comunicación personal.

PITUITARY GLAND IMPLANTATIONS IN RHEUMATOID ARTHRITIS

BY

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A report from the Arthritis Department in Lund (Edström and Westman, 1942) dealt with a case of malignant rheumatoid arthritis in a 20-year-old woman with endocrine disturbances (primitive amenorrhoea and alopecia totalis). This woman was treated in the years 1939-40 with triply repeated implantations of the anterior part of calf pituitary glands. The arthritic process, which had proceeded uninterruptedly for three years in spite of all therapeutic attempts, underwent a change immediately after the second implantation, the first having been made three months earlier with a less pronounced effect: the exudation and perioedema of the affected joints subsided almost entirely during the days immediately following, there was a lessening of the tenderness and articular aching, and stiffness of muscles and joints as well as of the " feeling " of infection and of illness. The sedimentation rate fell during the next few weeks to normal values and the patient's humour, appetite, and body-weight all improved. This improvement continued for about five years. A slight deterioration lasting a few months then made its appearance, after which there was a further complete abatement of symptoms. During the 10-year period of observation from 1939 the malignancy of the process has not returned, even though the patient still exhibits deficient function in some joints, especially the wrists, on account of the earlier destruction of some cartilage- and bone-surfaces. The improvement in her endocrine status was not of so high a degree, two small haemorrhages occurring, but no regular menses; on the other hand, she has had since 1939 a good growth of hair on the head and in the axillae, where there had previously been none at all.

After studying the experience of Hench and others (1949) and of Thorn and others (1949) respecting the effect of injections of adrenocortical hormones and pituitary adrenocorticotrophic hormone on rheumatoid arthritis this method has again been employed in the Arthritis Department at Lund.

Since August 1949, pituitary gland implantations of this kind have been carried out in twenty-six cases of rheumatoid arthritis. All these have been medium-severe, relatively fresh cases with a *duratio morbis* of from four months to four years. In one case use was made of the anterior part of a pituitary gland from a human foetus in the seventh gestational month; in all the others anterior parts of calf glands were employed, and two of these were implanted intragluteally at each operation, after being taken from the heads of the calves by a special sterile method, and so rapidly that not more than about 30 minutes elapsed from the calf's exitus

to the implantation of the substance, cut into pieces, in the buttocks. The operations were performed by A. Sjövall and assistants at the Gynaecological Department, Lund. Healing took place by first intention in all cases except seven; in these a suppuration arose after a few days, but healed in a short time. No immediate suppuration arose in any case. The operations were carried out under local anaesthesia. One to three implantations were made on each subject. (A more detailed account of the technique will be given in another connexion.)

The immediate effect obtained, when there was any effect at all, manifested itself as regards the clinical status in the following fashion. Even during the first 24 hours after the implantation there was a marked reduction of stiffness in joints and muscles. After some days there set in an improvement of the articular and muscular function, diminished aching and pains of the joints on motion, as well as reduced tenderness, peri-oedema and swelling of the joints. The patients did not feel so ill and had a better appetite, the sedimentation rate diminished slowly, and the same observation was made as at the adrenocorticotrophic hormone (ACTH) medication, viz. a slight euphoria with increased mental capacity and activity. (Moving pictures which were taken show this better.)

During the first 24 hours following the implantation there was in most cases a markedly increased excretion of 17-ketosteroids in the urine, though the values had already returned to normal after 24 hours (see Figure). It is open to discussion whether the increased excretion depends on ACTH or the gonadotrophic hormones in the implantates, though the small amount of the latter could hardly be responsible for the amount of the increase. At the same time the number of eosinophil leucocytes in the circulating blood was observed to diminish, this condition also giving

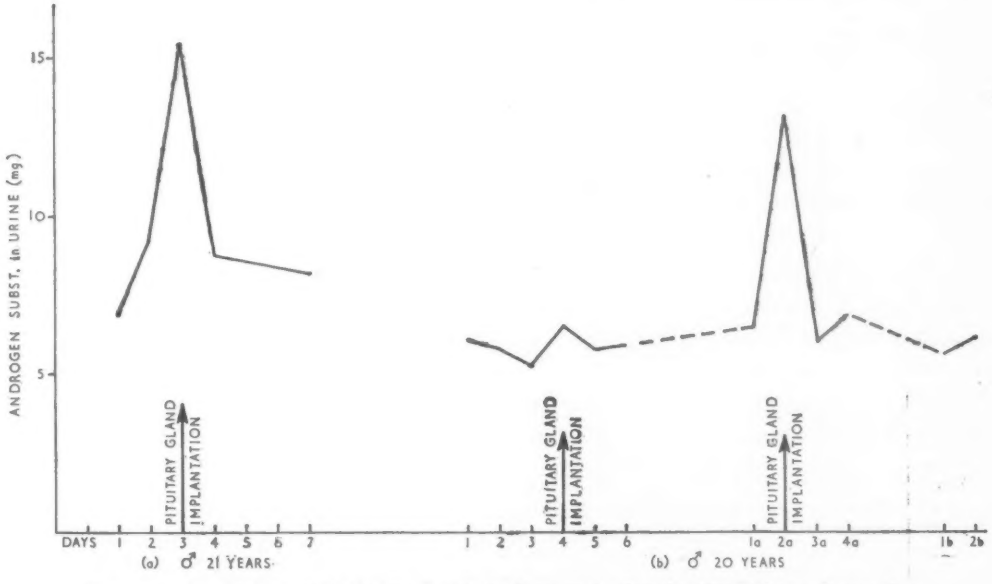

FIGURE.—Excretion of 17-ketosteroids before and after implantation of anterior parts of pituitary gland.

Case (a) man aged 21 years. Case (b) man aged 20 years.

place to normal values in a couple of days or so. No certain effect on the sodium, potassium, and chloride contents of the serum and on the plasma proteins has been observed.

In order to check that the operative trauma itself was not the active agent, a piece of brain without any pituitary body was also implanted under the same operative conditions. No effect was thereupon obtained on the clinical status, on the 17-ketosteroid excretion, or on the number of eosinophils in the circulating blood.

As Westman (1949) points out, in these pituitary gland implantations there can be no question of other than a transient hormonal shock or possibly of a short-time action of a hormone depot. The idea of a transplantation effect cannot be entirely rejected, for, as Westman and Jacobsohn (1940; 1942) have shown, the implanted pituitary glands are necrosed and absorbed rather quickly. That the hormonal effect thus obtained is of comparatively short duration and lasts for hardly more than a day, seems to be evident from our observations concerning the 17-ketosteroid excretion.

In this preliminary report it is as yet premature to express an opinion regarding any lasting effect that such an implantation may have upon the clinical status, the observation time being still too short for the majority of cases. In nine cases, however, the period of observation has been more than three months; an account of these cases is submitted in the following Table.

EFFECT OF PITUITARY GLAND IMPLANTATIONS ON RHEUMATOID ARTHRITIS

Case Nos. (in order of age)	Age (years)	Sex	*Duratio morbis*	Number of implantations	Effect of implantations		
					On clinical state	On blood sedimentation rate	
						1 hour before	1 hour after
344–49	20	m.	9 months	III	improved	94	13
334–49	21	m.	4 months	II	free from clinical symptoms	23	10
326–49	25	f.	3 years	III	,,	24	13
312–49	32	f.	1 year	II	,,	22	14
332–49	36	f.	2 years	I	,,	15	12
337–49	40	f.	4 years	III	,,	39	26
348–49	40	m.	1 year	II	no effect	34	67
333–49	45	m.	5 months	III	no effect	90	82
311–49	51	m.	1 year	I	free from clinical symptoms	38	12

Of the nine cases tabulated, six have been discharged from the department subjectively and objectively entirely free from symptoms in their joints, with a relatively normal sedimentation rate (between 10 and 14 mm. per hour, except in one case having a rate of 26 mm. per hour), and in good general condition. All these six patients are at their daily work. In two of these six (312 and 332) relapses have now occurred a little more than three months after the last implantations, but during that period of three months they were totally free from symptoms. Of the remaining three, one (344) has shown a considerable improvement, with diminished tenderness and stiffness in muscles and joints, less exudation and peri-oedema of the joints, no pain, and disappearance of a severe flexion contracture of the knee-joint, so that he is able to walk and run without trouble. His general condition is considerably better and his sedimentation rate has dropped from 94 to 13 mm. per hour, though he is not wholly free from symptoms. In the other two cases (333 and 348), men of respectively 40 and 45 years, no effect has been observed.

The immediate clinical effect in the seventeen other cases (not tabulated) is that nine have been totally free from clinical symptoms, and four have shown no effect.

An interesting observation is that in all the younger cases—under 40 years—a good clinical effect was obtained, while in the older cases the effect was not so pronounced. This is reminiscent of the experiments on rats of Silberberg and Silberberg (1939a, b; 1940), in which pituitary gland implantation produced a proliferation of articular cartilage in young animals while in older animals the effect ended in a mild degeneration of this cartilage.

The demonstration that injected adrenocorticotrophic hormone is very quickly excreted in the urine (within some minutes) has brought about a change in its use, so that several daily injections are now administered. As a result it has been found that full effect is also attained with a few mg. in each dose. That hormonal effect which is here obtained from these pituitary gland implantations appears to be produced by a hormone-depot effect from the implantate and seems to be equivalent to repeated small injections of this kind. In experiments with ACTH it has been found that the more injections given per day the lower both the single injection dose and also the total daily dose need be, in order to obtain full biological effect. This explains in its turn how the small amount of hormone contained in two injected calf pituitary glands can suffice to establish a biologically active hormonal effect for 24 hours or more.

The next question for discussion is how to explain that such a transient hormonal shock as is obtained from an implantation of this kind can produce a comparatively lasting effect on the clinical status. From the first reports relating to the effect of adrenocorticotrophic hormone in rheumatoid arthritis it seemed that it was relatively transitory in all cases, though it lasted at times some weeks after the conclusion of the treatment. All these cases, however, were selected malignant ones. Since that time milder cases also have been chosen for this treatment and it appears from the reports of Thorn and others (1949), Spies (1949), Markson and

Plum (1949), as though more lasting effects have also been observed by them in the less serious cases.

As yet it is too early to decide whether the effects here reported will be lasting or not. In six—possibly seven—of the cases the improvement has persisted for three months. All these, however, are milder cases without bone and cartilage destruction. On the other hand, however, in the malignant case with a 10-year period of observation first cited the effect has lasted these ten years.

Westman (1949) has given an account of the latest results obtained in a series of 246 cases of endocrine disturbance in which pituitary gland implantations were made and which were all under observation for at least one year after termination of the treatment. There was a lasting effect in 68 cases. Nystrand (1947) and Kylin (1937; 1943) report similar results, and similar results have also been obtained at other places in Sweden, although they have not been published.

One of the purposes of the pituitary hormones is, as we know, to give impulses to the more or less independent automatism of the other endocrine organs. A single pituitary hormone effect can therefore perhaps to some extent be likened to that obtained by winding the works of a clock; if it is a good clock it can continue to go quite a long time. Accidental causes may slacken the spring for a time. If these are overcome, the whole mechanism will come into good working order again.

What has thus far been found should stimulate further research. In addition, tests should be made to see whether further progress could be made with another implantation procedure, e.g. with combinations of adrenocorticotrophic hormone. Insulin chemistry has provided certain lines of guidance, but other paths are also conceivable. The use of implantation tablets of deoxycortone acetate (DOCA) in Addison's disease is a therapeutic gain of territory in certain morbid cases (Thorn and others, 1943; 1948). The conditions here may at times be analogous.

Summary

Ten years ago a twenty-year-old woman with malignant rheumatoid arthritis and endocrine disturbances was treated with implantations of the anterior part of calf pituitary glands with surprisingly good effect on the arthritis; the malignancy of the process has not returned during the ten-year period of observation.

Since August, 1949, twenty-six further cases of rheumatoid arthritis without endocrine disturbances have been so treated. All were relatively fresh cases of moderate severity. Nine have been observed for more than three months. Six were discharged from the Arthritis Department subjectively and objectively entirely free from symptoms in their joints, with a relatively normal sedimentation rate, a good general condition, and four of these are still employed in their daily work. One showed considerable improvement; two showed no effect. In all patients under 40 years the results have been good, but they are not so good in the older patients.

Where there was any beneficial result, it appeared immediately, and was similar to that exerted on the clinical state by ACTH medication: during the first 24 hours following the implantations there was a markedly increased excretion of

17-ketosteroids in the urine and a decrease in the eosinophils in the circulating blood.

Controls were made with implantations of brain without any pituitary gland.

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Implantations de la Glande Pituitaire dans l'Arthrite Rhumatismale

RÉSUMÉ

Il y a dix ans une femme de 20 ans souffrant d'une arthrite rhumatismale maligne accompagnée de troubles endocrines fut traitée par des implantations de la glande pituitaire antérieure de veau; l'effet favorable sur l'arthrite fut surprenant et au cours de dix années d'observation qui suivirent il n'y eut pas de rechute du processus maligne.

Depuis le mois d'août, 1949, on a traité de la même manière vingt-trois cas d'arthrite rhumatismale ne présentant pas de troubles endocrines. Tous ces cas furent relativement récents et modérément sévères. Neuf cas furent observés pendant plus de trois mois. Six furent renvoyés du Département Arthrologique de Lund, débarrassés de tous les symptômes articulaires objectifs et subjectifs, avec leur sédimentation globulaire relativement normale et en bon état général; ils poursuivent encore leur occupation normale. Il y eut une amélioration considérable dans un cas; aucun effet dans deux cas. Chez tous les malades relativement jeunes (moins de 40 ans) les résultats furent bons, mais ils ne furent pas aussi bons chez les plus âgés.

Tout résultat favorable apparaissait immédiatement et il ressemblait à celui obtenu par suite de l'administration de l'hormone adrénocorticotrophique en ce qui concerne l'état clinique: pendant les 24 heures qui suivirent l'implantation il y eut une excrétion urinaire sensiblement accrue des 17-cétostéroides et une diminution des éosinophiles dans le sang circulant.

On implanta aix témoins des fragments de cerveau sans glande pituitaire.

Implantaciones de la Glandula Pituitaria en la Artritis Reumatoide

RESUMEN

Hace diez años una mujer de 20 años sufriendo de artritis reumática maligna con disturbios endocrinos fué tratada por implantaciones de la glándula pituitaria anterior de ternero; el efecto favorable fué sorprendente y durante los diez años de observación que siguieron el proceso maligno no volvió a repetirse.

Desde agosto de 1949 se ha tratado de la misma manera 23 casos de artritis reumatoide sin disturbios endocrinos. Todos los casos fueron bastante recientes y moderadamente severos. Nueve casos estuvieron bajo observación durante más de tres meses. Se ha dado de alta del Departamento de Artritis de Lund a seis de ellos, librados de todos síntomas articulares, objetivos y subjetivos, con la sedimentación globular relativamente normal y en buen estado general; todos continuan sus ocupaciones normales. Hubo una mejoría considerable en un caso, ningún efecto en dos. En todos los enfermos relativamente jóvenes (menos de 40 años) los resultados fueron buenos pero no lo fueron tanto en los más viejos.

Siempre que hubo un resultado favorable, éste aparecía inmediatamente y se parecía por el estado clínico a los obtenidos por la administración de la hormona adrenocorticotrófica: durante las 24 horas que siguieron la implantación hubo una excreción urinaria marcadamente acrecida de 17-cetosteroides y una diminución de los eosinófilos en la sangre circulante.

Se implantó a los testigos fragmentos de cerebro sin glándula pituitaria.

INVESTIGATIONS INTO PERIPHERAL CIRCULATORY AND METABOLIC PHENOMENA*

ON THE "REDUCTION TIME" OF THE BLOOD OF THE SKIN AND ITS RELATION TO THE BASAL METABOLISM OF THE ORGANISM

BY

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The campaign against a widespread disease often makes apparently insuperable demands on the strategic power of the combatants, chiefly because their knowledge of the enemy is insufficient. Man has repeatedly given up this struggle because the problem seemed insoluble but, from time to time, tenacious energy has been rewarded with success and has brought a solution, or at any rate a rapid advance towards one. For instance, in the half-century since the discovery of the tubercle bacillus, the lethal power of tuberculosis had been reduced to less than one-tenth; this result was achieved before we had succeeded in finding a certain remedy for the disease, by close examination of its nature and mode of action, and thus we have managed to create a scientifically well-founded rational prophylaxis—which is the ideal procedure.

The study of the aetiology and pathogenesis of the rheumatic diseases is now the principal task of rheumatological research. At present we are confronted with a group of disorders which bear a close resemblance to a large and complicated jig-saw puzzle in which some of the pieces have already been put in their proper places, others are at our disposal, but unplaced, and others again are entirely missing. As a consequence of recent research, the study of the peripheral vascular system will become of importance in the study of the rheumatic diseases (van Breemen, Dautrebande, Laignel-Lavastine, Pemberton). Otto Meyer considers that infectious foci give rise to considerable functional disturbances of the large vessels, and he draws attention to Bauer's results which show that in the rheumatic articular affections histological changes occur in the numerous fine vessels of the synovial membranes.

The nature of these changes has not been fully explained. Among other things it has not been settled whether they are primary vascular changes or whether they are secondary in relation to changes of the vegetative nervous system, its peripheral or central parts. Considering that thought is tending away from Virchow's cellular

* Read in summary before the Seventh International Congress on Rheumatic Diseases, New York, June 1, 1949.

pathology and towards Ricker-Speransky's neural pathology, it can at any rate be taken for granted that the study of the anatomy, physiology, and pathology of the peripheral vessels will render possible the employment of the phenomena of peripheral circulation and metabolism as indicators of the condition of the entire vegetative system and its role in the local processes. The solution of this problem will not, of course, lead to the solution of the rheumatic problem, but it is highly probable that this solution represents a missing piece—and a very important one—in the jig-saw puzzle.

The study of the peripheral circulation has been rather stagnant since, more than twenty-five years ago, the Danish Nobel Prize winner, August Krogh, published his famous works on the anatomy and physiology of the capillaries. During the second world war the problem was taken up in different countries and for various reasons but, as conditions were, no co-operation was established until the end of hostilities. A number of different investigators took up the problem for very different motives. No detailed account will be given of the various methods that have been suggested for the examination of the peripheral vascular phenomena, but we shall confine ourselves exclusively to the study of the minutest vessels, even though it must be admitted that a more active physiological importance than has hitherto been imagined must apparently be attributed to the large arteries and veins. It is first and foremost the most peripheral phenomena that are of interest in the study of the rheumatic problem.

With various co-workers we have since 1942 been at work on these problems, and have attempted to elaborate methods for the study of the phenomena of peripheral circulation and metabolism. We have on previous occasions accounted for the so-called digitographic pulse-recording method and also for our electrophotometric pulse recording, which has been considerably improved since one of us (E.J.) became acquainted, during his stay in the U.S.A. in 1946, with the works of Hertzmann and his co-workers, which had not previously been available to us because of Denmark's isolated position during the German occupation.

For peripheral pulse recording we now employ an apparatus which is highly simplified and can be used all over the body (Jarløv and Gravenhorst, 1948). The same apparatus is employed to determine the amount of oxygen given off by the blood in the skin, but such determinations can be made only on extremities where it is possible to induce arterial stasis.

Description of Apparatus

The apparatus consists of a photo-electric reflectometer (Fig. 1) and a measuring instrument (Cambridge spot-galvanometer) which is provided with a compensation device, enabling the examiner to compensate for the resting potential of the photo-cell and thus to have a " wider galvanometer range " at his disposal, which gives a safer reading. Fig. 1 shows a diagram of the photo-electric galvanometer, which consists of: A, a source of light (a 6-volt bulb); C, a selenium photo-cell (" Eel ", type A) with an opening 9 mm. wide in the central part; B, a sliding filter-holder with red and green filters (" Wratten " gelatine filters, Nos. 29 and 61). When the instrument is placed on the surface of the skin the light rays from the bulb, A, will pass through the filter and be reflected from

the surface of the skin, D, to the side of the photo-cell that is sensitive to light and faces the skin. The electrical impulses of the photo-cell are recorded by means of the galvanometer. The filters have been selected with consideration of the differences between the absorption spectra of oxyhaemoglobin and reduced haemoglobin, so that, with the red light, the greatest possible difference of reflection is obtained when the haemoglobin passes from the oxidized state to the reduced state, whereas the reflection of the green light remains uninfluenced by this process (Millikan).

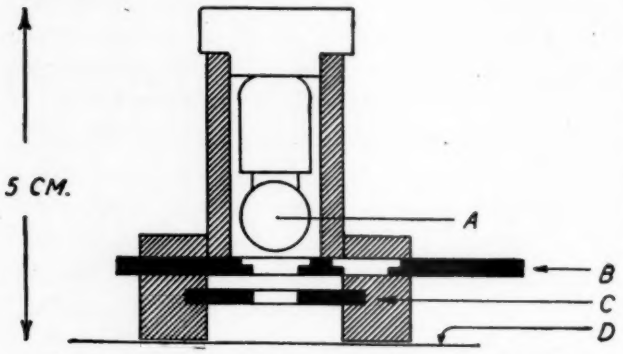

FIG. 1.—Diagram of the photo-electric reflectometer.

The examination of the reduction of oxyhaemoglobin under arterial compression is made as follows: the subject is placed in the sitting posture with one upper extremity in the horizontal position at the level of the aortic orifice. The reflectometer is placed in his palm, proximally in the hypothenar region. A sphygmomanometer cuff is applied to the upper arm and sudden and complete arterial compression is produced for about two minutes. If the reflection of red light is determined during this period, a distinct decrease will be observed. After about two minutes' compression the green filter is inserted, and the deflection of the galvanometer will indicate the degree of fullness of blood in the skin, as the reflection of the green light remains uninfluenced by the degree of oxidation of the blood (the haemoglobin), and is influenced only by the amount of blood present in the superficial layers of the skin. The change of reflection for red light during arterial compression is reproduced in Fig. 2 (opposite), where H expresses the intensity of the reduction of oxyhaemoglobin or, in other words, the oxygen consumption of the tissues of the skin. In addition, H is influenced by the temperature of the tissues and by the amount of blood present in the skin during the experiment. Immediately before every examination the temperature of the skin is determined thermo-electrically and, as already mentioned, the amount of blood is expressed by means of the reflection of green light, but the ultimate factor of correction to " standard temperature and standard amount of blood " has not not been quite fixed. As will appear from the following, these corrections will be of only minor importance under normal conditions.

So far we have not attempted any determinations on mucous membranes, which, however, should theoretically be possible; it must also be considered possible to employ a similar apparatus in examinations of other organs in animal experiments. Our object is to create methods which can be employed in clinical work, enabling us through clinical examinations to find out what organs are affected, what kind of disturbances are present, what information this will give us, and what are the possibilities of experimental work in a number of different domains, among others in the domain of rheumatology.

By studying for the present the conditions of peripheral circulation and metabolism in the skin we believe we can become informed both of the functions of the organs of circulation and of those of the skin. The examination of the reactions of the peripheral vessels may possibly provide the basis of understanding a number

of rheumatic problems and, at the same time, through the study of a number of individual reactions to cold, heat, pain, psychic impressions, etc., supply us with objective criteria to judge the treatment of the individual case.

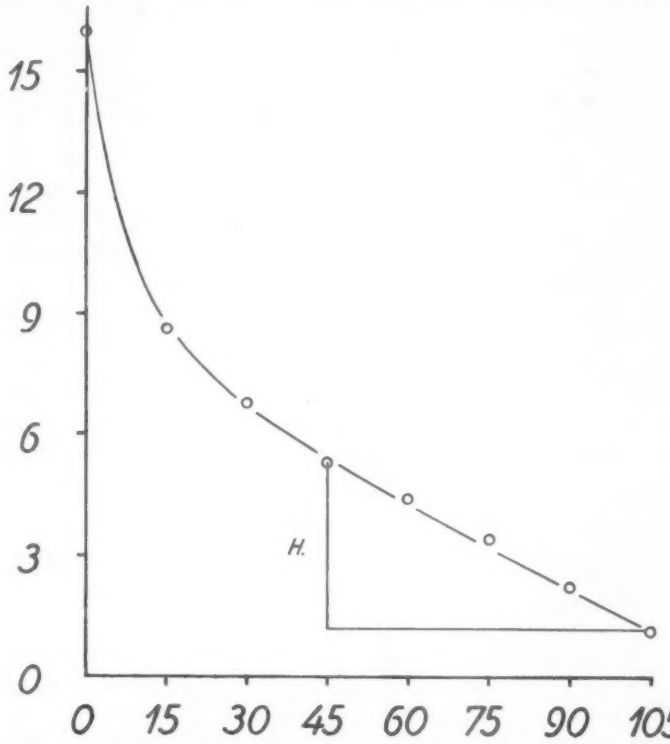

FIG. 2.—Change of reflection for red light during arterial compression.

At the same time it is highly probable that these examinations may prove an aid to estimating the functional condition of the skin as an organ—a condition to which we attribute much greater importance nowadays than formerly, when the skin was *a priori* considered to be simply a protective cover over the functioning organs, being only reckoned as a thermo-regulator acting through its circulatory system and its system of sweat glands. It is true that it has been realized for many years that through the " insensible perspiration " the skin also acts as a water-excreting organ. Nowadays, however, many investigators consider that the skin has a series of other functions, among other things that it plays an important role as endocrinous organ and in the formation of antibodies in infections, in particular in the production of diphtheria antitoxin. We shall not deal with modern theories of the function of the skin in fuller detail; the role of the skin in general pathology was recently discussed by P. Robert (1949).

However, it is not the vascular reactions themselves that are important, but the exchange between blood and tissue. As is known, modern functional diagnostic methods have caused determinations of metabolism to be a daily procedure in clinical work, but almost exclusively in the sense of determinations of basal metabolism; so far we have not had any great possibility of estimating clinically the local oxidation processes and the intermediary metabolic processes. It is an attempt in a single field of this domain that we shall describe here, namely the determination of the oxygen consumption of the skin and the relation of this process to the metabolism of the entire organism. We have been working on this problem since 1943,

but owing to the war and other hindrances we could only follow it up to a small extent until the past few years. Our plan was to determine the reduction of the blood of the skin by means of its change of colour as observed by electrophotometrical methods during the first few minutes after induction of complete arterial stasis, an idea which was then considered by us to be quite new; but, when literature became available, it appeared that Ray and others (1946) in America had entertained the same idea and had determined the reduction of the blood spectrometrically. The American investigators stated that through studies of the literature they were surprised to find that the self-same idea had been conceived by Vierordt as early as 1878.

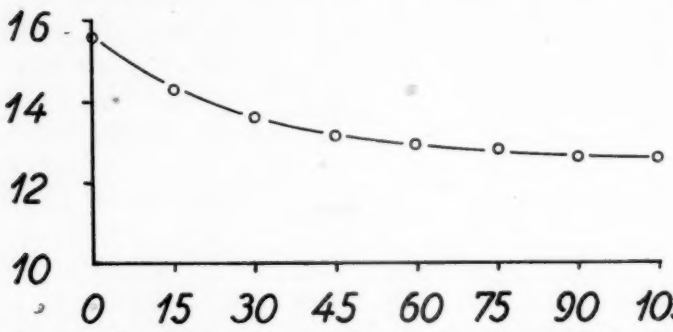

FIG. 3.—The reflection of green light, determined immediately after induction of the complete congestion.

Vierordt's procedure was briefly as follows: By means of a spectroscope he was able to observe the absorption spectrum of haemoglobin when he studied the skin of a finger under high transillumination. He then interrupted the circulation of the finger by constriction with rubber rings, and determined the time which elapsed before the two characteristic absorption bands of oxyhaemoglobin between the D and E lines disappeared (" the reduction time "). In a subsequent work by Vierordt's pupil, Dennig (1883), the dependence of the reduction time on the temperature of the skin was demonstrated. On the basis of a number of examinations Vierordt, as early as 1878, maintained: " Die Untersuchung des Absorptionsspectrums des in den Gefässen enthaltende Blutes am Lebenden, vor allem am Menschen selbst, verspricht wesentliche Aufschlüsse über die Stärke des jeweiligen Sauerstoffverbrauchs im Körper . . ."

When it is intended to work with such a method we must, as in all other similar examinations, attempt to clear it of sources of error. Among these we have so far reckoned with the following: with a sudden arteriovenous stasis the arterial pressure will fall and the venous pressure will rise, whilst at the same time the conditions of pressure in the capillaries will become abnormal; especially after some time, when the arterial and venous pressures have become equalled, the pressures at the arterial inflow and the venous outflow of the capillaries will be alike, in contrast with the physiological conditions. Thus the results cannot be directly compared with the result of the reduction of the blood in the case of unobstructed flow through the capillaries. The interruption of the circulation, moreover, causes the supply of oxygen to the tissues to decrease abnormally, which after some time must necessarily lead to abnormal conditions of the tissue cells.

The first source of error has been studied by Wilkins and Bradley, who found

that the difference of pressure was equalized after about 45 seconds, which is in conformity with an observation made by us.

Fig. 3 shows the reflection of green light, determined immediately after induction of the complete congestion; it will be seen here how the amount of blood in the vessels of the skin increases during the first 45 seconds or so, and then remains almost constant during the rest of the examination, in complete conformity with the results of Wilkins and Bradley.

Therefore, we do not consider the changes occurring in the course of the first 45 seconds.

The second source of error hardly plays any great part, as it should be borne in mind that the amount of oxygen given off to the tissues is dependent on the oxygen tension of the plasma, and this will tend to adjust itself by the blood corpuscles giving off more of their oxygen to the plasma. It is not probable that this process will bring about complete compensation, but, owing to the short duration of the experiment, it is hardly possible that any significant error will be involved for this reason.

A third and important source of error is afforded by the natural colour of the skin and the amount of blood present in it. We first determine the latter by measuring the reflection of green light within the wave-lengths about 500$\mu\mu$. For this reflection will be entirely dependent on the amount of blood present in the skin, while the pigmentation, of course, will be the same at the beginning and at the end of the experiment, and, consequently, is of no significance (in this connexion, however, we can only speak of white people without any great abnormal changes of the skin).

As the stasis induced causes a certain reactive hyperaemia, we start the examination with the induction of two or three minutes' complete stasis, and finish every experiment with a determination of the " green rate ", which, with this procedure, is practically the same before and after the determination.

As it appears that the amount of blood present in the skin, the pulsation, and the quantity of oxygen given off vary at different temperatures of the skin, a thermo-electrical determination of the temperature forms an indispensable part of the examination, and a correction for this must be introduced; under normal circumstances this correction plays a very small part, but with extreme values the deviations become very great.

A purely technical source of error may be caused by variations of candle-power. This can be eliminated by inserting a resistance between the source of light and the battery, and by letting the bulb burn for about twenty minutes before the determination begins. Nevertheless, quite slight variations of the candle-power may occur, and therefore we control it before and after every experiment by placing the photo-cells apparatus, with the source of light burning, on a grey dull metal plate and making corrections for the small differences that may appear in the deflection in this control test.

Lastly, there is the question of the experimental conditions under which the metabolism of the skin is to be determined, and this again must be linked up with

the question of the relation of the metabolism of the skin to that of the rest of the organism. As is known, a certain and very material part of the metabolism of the organism is going on in the muscles, which is one of the difficulties with which the determination of the basal metabolism in clinical work is connected, as such a determination requires the patient to be in a state of absolute muscular rest. But this is very difficult to achieve, in particular in nervous individuals, and in many cases, especially in fat people, the work of respiration itself in the recumbent posture will undoubtedly cause the metabolism to be at so high a level that it is not the basal metabolism itself we determine. The question is, then, how the skin behaves in this respect. It is generally supposed that here the skin is rather passive, and for the present our examinations suggest that the metabolism of the skin in the individual person is strikingly constant when major influences of heat and cold, pain and psychic impressions are avoided. That the last-mentioned influence plays a part appears solely from the fact that Burch of New Orleans and his co-worker, Ray, found that vigorous psychic impressions cause considerable variations in the pulsation of the fine vessels of the skin. Burch, therefore, terms the peripheral vascular system the finest " effector organ " in the psychosomatic processes.

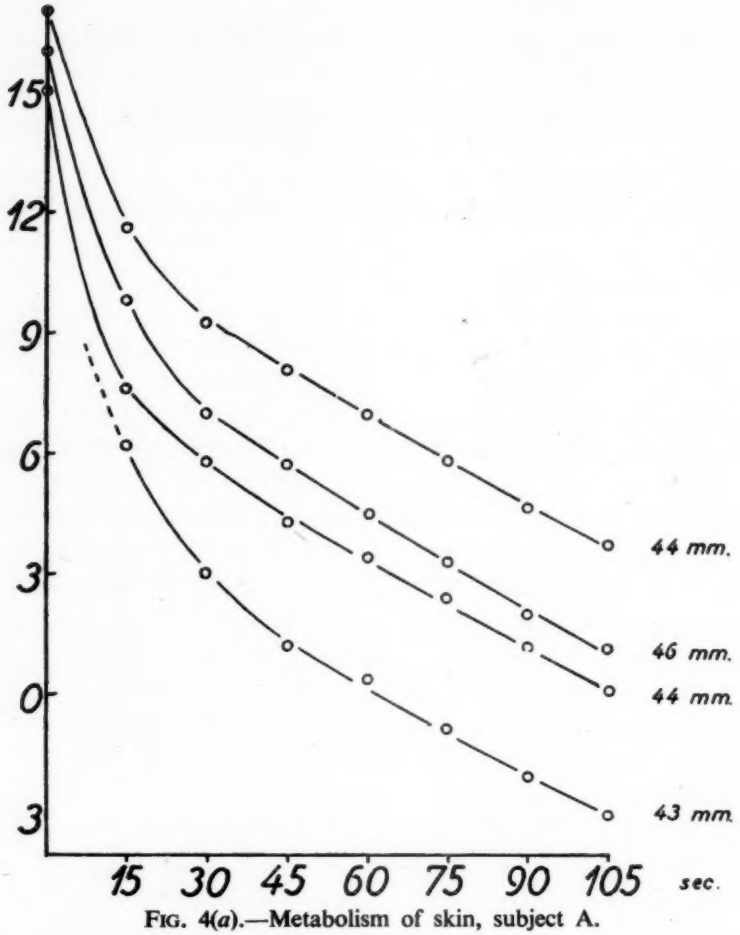

FIG. 4(*a*).—Metabolism of skin, subject A.

Whilst major influences of the nature mentioned above will thus have to be avoided in these examinations, it seems as if—in contrast with the determinations of metabolism hitherto employed—the muscular work and the ingestion of food play no part in the metabolism of the skin, which we have determined in subjects at

highly varying distances from meals, and before and after strenuous muscular work, without having been able so far to demonstrate any influence on the metabolism of the skin, which remains surprisingly constant in the same individual in determinations under the varying conditions mentioned. Thus, in the course of about six months, we have made a long series of determinations in two persons of different age, always finding the same values in the same person, though the metabolism of the skin of each subject displayed a certain difference one from the other (Figs 4*a* and 4*b*).

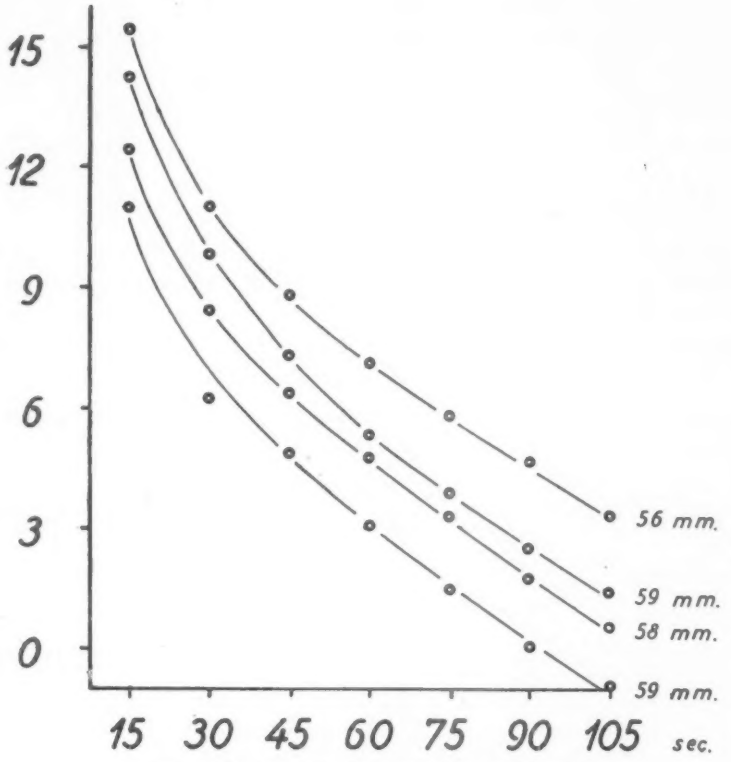

FIG. 4(*b*).—Metabolism of skin, subject B.

In examinations of patients we found similar conditions, but it has not been possible for us to follow them for so long a time. The question is, then, whether this metabolism of the skin is parallel to the basal metabolism of the individuals in question. This was taken for granted in advance by Vierordt when he made his examinations, but apparently he did not realize what sources of error one would have to reckon with. Still, it appeared in our examinations that there is a certain parallelism between the metabolism of the skin and the basal metabolism, as will be seen from the diagrams, which show the " reduction time " of the individuals in question in relation to their basal metabolism as determined by means of Krogh's method. It may be mentioned in this connexion that in hyperthyroid processes there is a decreased reduction time in some cases, but this is not a decrease that is completely parallel to the basal metabolism determined. This may, however, possibly be explained by one case, namely that of a young woman in whom had been found an increase of 38 per cent., whereas our examinations showed a normal reduction time. When the determination was repeated, the basal metabolism was increased by about 20 per cent., and the reduction time was unchanged, but at the third determination the basal metabolism was normal and the reduction time

remained unchanged. It is probable that the ordinary determination of the basal metabolism in patients with toxic goitre gives too high values because of the nervousness of the patients, and that this phenomenon is reflected to a less degree in the reduction time, but a greater number of examinations will be required to settle this and the question of the relation to the basal metabolism in general.

Having now worked for five years with this technique, we are of opinion that the apparatus has been simplified as much as possible. It has been assembled in such a manner that it is possible in a very short time to record by means of the same apparatus the pulsation of the vessels of the skin, the temperature of the skin, and the reduction time of the blood of the skin. This paves the way for other examinations of the condition of the minutest vessels in a number of different diseases, including the rheumatic diseases, and for an estimate of the importance of the function of the blood vessels to the tissues, and at the same time it renders possible a control of the effect of physio-therapeutical interferences. Further, it is possible that these examinations, which require very little co-operation on the part of the patient and do not cause any inconvenience, may be used as a rapid technique in arriving at an estimate of the basal metabolism in cases where it cannot be determined by means of the usual methods because of anxiety, impaired general health, or the like.

Summary

The pulsation of the tiniest cutaneous vessels can be registered "digitographically" (that is, plethysmographically) and electrophotometrically.

Our electrophotometric apparatus has been modified for measuring the desoxidation of the blood in the skin capillaries during the first three minutes after establishment of arterial stasis.

By repeated measurings in one individual the "skin metabolism" (after correction in regard to the skin temperature) is found remarkably constant.

The "skin metabolism" on the other hand is different in different individuals. A certain parallelism seems to exist between the "skin metabolism" and the standard metabolism of the organism.

Measurements carried out by this technique may possibly be of importance to rheumatological research, in controlling physiotherapy, and in other fields of physiology and medicine.

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Les Phénomènes Circulatoires Périphérales et Métaboliques

RÉSUMÉ

La pulsation des plus petits vaisseaux peut être enregistrée en manière digitographique (c'est à dire, pléthysmographique) et électrophotométrique.

Notre appareil électrophotométrique a été modifié pour la mesure de la désoxydation du sang aux capillaires cutanés pendant les trois premières minutes après l'établissement de stase artérielle.

Par une série d'expériences sur le même sujet " le métabolisme cutané " (correction faite pour la température de la peau) s'est trouvé être singulièrement invariable.

Par contre le " métabolisme cutané " varie d'un sujet à l'autre. Il paraît être un certain parallélisme entre le " métabolisme cutané " et le métabolisme basal de l'organisme.

Peut-être des mesures faites par cette méthode seront-elles d'importance pour les recherches rhumatologiques, pour le contrôle de la physio-thérapie, et dans d'áutres domaines de la physiologie et de la médecine.

Los Fenomenos de la Circulación Periferale y los Fenomenos Metabolicos

RESUMEN

Las pulsaciones de los vasos cutáneos más diminutos pueden registrarse " digitográficamente " (es decir pletismográficamente) y electrofotométricamente.

Nuestro aparato electrofotométrico ha sido modificado para que pueda medir la desoxidación de la sangre en los capilares del cutis durante los tres primeros minutos posteriores al establecimiento del estasis arterial.

Repetidas medidas tomadas en un mismo individuo han mostrado que el " metabolismo cutáneo ", después de haberlo corregido en relación con la temperatura de la piel, es notablemente constante.

Por otro lado el metabolismo cutaneo es diferente en los diferentes individuos. Parece que existe cierto paralelismo entre el "metabolismo cutáneo" y el metabolismo básico del organismo.

Es posible que las medidas hechas por este procedimiento puedan asistir considerablemente en los trabajos de investigación reumatológica y en el control de la fisioterapia, así como en otras esferas de la fisiología y de la medicina.

GLYCINE IN THE TREATMENT OF GOUT

BY

FRED WRIGLEY

The use of glycine and salicylate in the treatment of gout has now become fairly well established. This paper is to suggest a reconsideration of this form of therapy. Quick (1934), writing on " Uric Acid in Clinical Medicine ", says: " Of prime importance is the observation that under standardized and fixed conditions, the rate of uric acid excretion tends to be constant, is uninfluenced by the volume of urine, and is independent of the concentration of uric acid in the blood." The rate of uric acid excretion seems, therefore, dependent upon a metabolic process. Unlike creatinine, which is promptly excreted when fed, uric acid ingestion does not increase the hourly output. Quick then lists substances which increase and

TABLE I

EFFECT OF SALICYLIC ACID AND OF ACETYLSALICYLIC ACID ON URIC ACID EXCRETION. SYNERGISTIC ACTION OF GLYCINE

Salicylic acid taken	Uric acid excreted (mg.)					Total in 24 hours
	1st hour	2nd hour	3rd hour	4th hour	5th hour	
0	23·0	23·2	22·1	20·5		480·0
0 with 15 g. gelatin	29·3	33·1	29·2	17·5		
0·5 g.	21·4	23·4	21·0			
0·5 g. with 3 g. glycine	18·7	26·0	23·0			
0·57 g. as acetylsalicylic acid* ..	19·5	22·1	22·8			
0·6 g. intravenously	34·3	24·5	22·4			
1·0 g.	27·2	36·0	38·3	31·8	23·0	
1·0 g. with 15 g. gelatin	30·0	48·1	35·0	18·0	23·1	
1·15 g. as acetylsalicylic acid† ..	25·5	41·0	34·5			
2·0 g.	30·6	41·0	40·0	33·8		765·0
2·0 g. with 1·5 g. glycine	47·0	49·9	39·6			
2·0 g. with 3 g. glycine	46·0	56·5	50·5			
2·0 g. with 15 g. gelatin	43·3	56·0	49·1	42·0	48·2	
3·5 g.	35·2	58·5	45·5	44·0		
3·5 g. with 15 g. gelatin	57·7	85·6	77·0	68·5		757·0

* 0·008 g. of salicylic acid as acetylsalicylic acid excreted during the first hour.
† 0·014 g. of salicylic acid as acetylsalicylic acid excreted during the first hour.

decrease uric acid output. Amongst those said to increase uric acid output is glycine.

Quick (1933) reported the results of a very interesting and careful study and explained that there appeared to be a synergistic action between glycine and salicylic acid which should find therapeutic applications. His results are given in Table I. Unfortunately the parallel figures for the blood uric acid are not given.

The effect of glycine on the production and excretion of uric acid has been considered and discussed by Friedmann (1947). Although most people are agreed that ingestion of protein increases the output of uric acid in man, no one has yet made it clear why this takes place. Mares (1910) thinks that deterioration of the digestive cells concerned in the assimilation of ingested protein is responsible for increased urinary uric acid output following high protein feeding.

Taylor and Rose (1914) found that although uric acid excretion increased after protein intake, urinary creatinine did not change.

Dunn and others (1918) fed different amino acids to man and found that all those tested, except sarcosine, increased the output of uric acid and because this substance is not catabolized in the body, these workers suggest that the increased uric acid output after high protein diet was due to generalized cellular stimulation following the higher calorific intake.

Christman and Mosier (1929) administered glycine to several subjects and demonstrated that urinary uric acid was increased, but there was no change in the urinary excretion of creatinine. They agreed with Rose (1921) about the general stimulating effect of amino acids on metabolism, and the secondary increase of uric acid.

None of these investigators appears to have determined the concentration of blood uric acid after ingestion of amino acids, and it has merely been assumed that such a rise occurred because of the increased urinary output observed. Gibson and Doisy (1923), however, did not detect a rise in blood uric acid in man after the feeding of amino acids. Pitts (1943) showed that an excess of glycine might influence the renal excretion of a blood constituent by competing with it in the excretory system.

Friedman (1947) did both animal and human studies with glycine, but unfortunately he only treated two men. His results with the rat showed that increased uric acid output resulted in 17 of the 19 rats studied, the average uric acid output being 0·136 mg. per hour before glycine was ingested, and 0·170 mg. per hour afterwards. Thus there was an increase of 25 per cent. in uric acid output and the uric acid clearance also increased by about 35 per cent. The average volume decreased and the average creatinine clearance showed no significant change, and from these studies it was inferred that the increase in uric acid output after glycine ingestion is due neither to increased glomerular filtration, nor to increased renal blood flow. As far as the blood was concerned an increase of the blood uric acid took place in the control rats, and a similar increase was found in those rats given glycine (see Table II, overleaf). From this it is assumed that glycine *per se* does not increase the production of uric acid in the animal body.

TABLE II
THE EFFECT OF GLYCINE ON BLOOD URIC ACID IN THE RAT

	Normal rat			Normal rats given glycine*		
Time	10 a.m.	12 noon	3 p.m.	10 a.m.	12 noon	3 p.m.
Average blood uric acid in mg. per cent. ..	0·97	1·16	1·51	0·91	1·21	1·44

* Each rat given 50 mg. of glycine per 100 g. body-weight at start and then 5 mg. every hour of the 5-hour study period.

Experiments were also conducted on nephrectomized rats. The average blood uric acid level of 8 control rats before nephrectomy was 1·85 mg. per 100 cc. of blood; 24 hours after nephrectomy the blood concentration was 1·88, and it was 1·96 48 hours after; this represents an increase of 6 per cent. in the blood uric acid 48 hours after nephrectomy. Nine rats were given glycine after nephrectomy, and the blood uric acid level, which was 1·71 before nephrectomy, was 1·80 after 24 hours and 1·84 after 48 hours, representing an increase of only 8 per cent. Thus it might be said that the feeding of glycine did not significantly raise the blood uric acid level of this group of rats; but since the rat converts uric acid into allantoin and any excess uric acid produced in these nephrectomized rats may have been so quickly converted to allantoin that no rise in blood uric acid occurred, the experimental data obtained from these nephrectomized rats cannot safely be applied to human subjects.

In the human experiments (see Table III) the ingestion of 25 grammes of glycine by two subjects was found to increase the uric acid output of both. The average uric acid output was 23·4 mg. per minute before the administration of glycine,

TABLE III
THE EFFECT OF GLYCINE ON BLOOD URIC ACID AND URIC ACID EXCRETION IN MAN

Subject	Blood uric acid in mg. per cent.			U.V.	C.C.	U.A.E.	U.A.C.
	10 a.m.	12 noon	3 p.m.				
Before glycine :							
1.	3·20	3·10	3·10	3·95	115	19·20	10·30
2.	3·40	3·40	3·50	2·56	118	27·60	13·50
Average ..	3·30	3·25	3·30	3·26	116	23·40	11·90
*After glycine (25g.):							
1.	3·60	3·60	3·90	2·50	100	35·60	16·10
2.	4·00	3·90	3·90	2·48	101	44·30	18·90
Average ..	3·80	3·75	3·90	2·49	100	39·95	17·50

U.V. = urine volume in ml. per minute.
C.C. = creatinine clearance in ml. per minute.
U.A.E. = mg. of uric acid excreted in urine per minute.
U.A.C. = uric acid clearance in ml. per minute.
* Glycine given after the 10 a.m. blood sample had been obtained.

and 39·95 mg. after, an increase of 71 per cent. Similarly, the average uric acid clearance increased from 11·9 to 17·5 ml. per minute, an increase of 47 per cent. As was observed in the rats, the average urinary volume also decreased from 3·26 ml. per minute before to 2·49 ml. after glycine, and the average creatinine clearance also decreased. Little or no change was observed in the blood uric acid level after glycine had been given.

These results lend colour to the suggestion that glycine does not increase the production of uric acid in the body of either rat or man; but it does not appear certain that glycine ingestion increases the renal excretion of uric acid, and it must be borne in mind that studies of creatinine and hippurate show clearly that there is no increase in the rate of glomerular filtration nor in the renal blood flow. Thus the author concludes that glycine probably impedes tubular re-absorption in some manner; in other words, that the uric acid output is increased, not because the kidney filters or secretes more of it, but because the tubules re-absorb less of it in the presence of excess glycine. Despite this explanation one can see throughout all these studies that the blood uric acid failed to *decrease*, but that in fact it actually *increased* a little, in spite of the increased renal output.

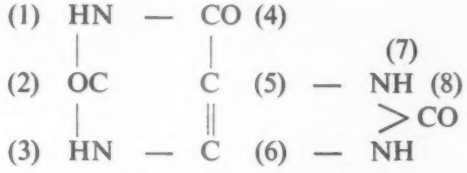

FIG. 1.—Uric Acid.

One might think there is not in these studies sufficient evidence to justify the administration of glycine to a case of gout. Later evidence points to the fact that the administration of glycine may actually promote the formation of uric acid.

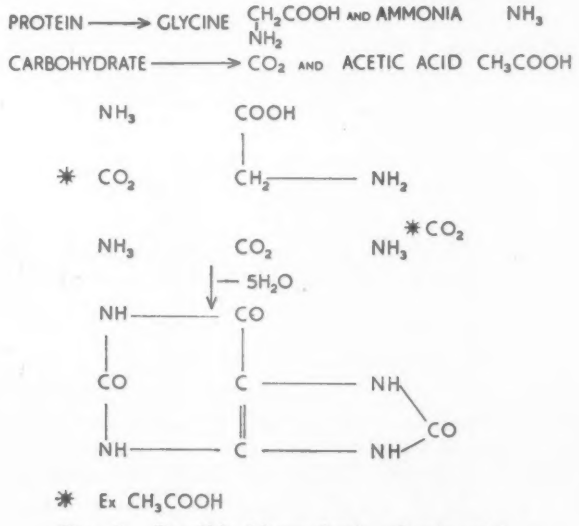

FIG. 2.—Possible biosynthesis of uric acid.

Shemin and Rittenberg (1947) have shown in human subjects: (1) that glycine contributes nitrogen to position 7 in uric acid; and (2) that also in all probability carbon atom 5 is derived from the d-carbon atom of this amino acid.

Sonne and others (1946) worked on metabolism in the pigeon and pointed out that glycine, or a metabolic derivative of it, is probably the precursor of the C atoms 4 and 5 in uric acid. The data obtained also leads them to think that CO_2 is the precursor of C atom 6 and that the carboxyl carbon of acetate is the precursor of carbons 2 and 8. A strictly diagrammatic representation of what may take place is shown in Fig. 2.

The ideas reviewed above are set out in the hope that further metabolic studies will be undertaken in normal and gouty patients, obtaining both blood and urinary uric acid figures. It may well be that if red cell and plasma uric acid is estimated we shall obtain useful information. In any case an attempt should be made to show what glycine really does and to determine its place in the treatment of gout.

Summary

The suggestion is advanced that the use of glycine in gout should be re-considered. The work leading up to its employment in this disease is discussed. It is pointed out that isotope studies have shown that glycine contributes some of the prosthetic groups for uric acid.

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Glycine et Goutte

RÉSUMÉ

On suggère que l'emploi de la glycine dans la goutte doit être reconsidérée. On discute les travaux qui ont mené a son application dans cette maladie et on indique que l'étude des isotopes a montré que la glycine contribue certains groupes prosthétiques à la formation de l'acide urique.

La Glicina y la Gota

RESUMEN

Se sugiere que la cuestión del empleo de la glicina en la gota merece una revisión. Se discute los trabajos que condujeron a su empleo en esta enfermedad y se señala que el estudio de los isotopes ha mostrado que la glicina contribuye ciertos grupos prostéticos a la formación del ácido úrico.

RHEUMATIC POLYTENDOVAGINITIS

BY

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Inflammatory changes in the tendon sheaths are recognized as a common accompaniment of many rheumatic diseases (Sperling, 1949). In rheumatoid arthritis this is a part of the general rheumatic involvement. Baumgartner (1946) pointed out that the rheumatic picture may present itself primarily with tendon sheath involvement. This picture is apparently rare, with few reports in the literature. For that reason the following case history is given in detail.

Case History

The patient, a 45-year-old white, married man, was first seen on Nov. 12, 1948, with a fifteen-year history of progressive development of nodulations over the finger joints, thickening of the palms, and generalized joint pain. The history revealed nothing important, and there had been no gonorrhoea. He had been a heavy drinker for many years, but had stopped five years previously. He was a mechanical engineer, but had recently, up to the time of his hospitalization, worked as a house painter.

Fifteen years previously he noted a swelling over the dorsum of the proximal interphalangeal joints of the right index finger. This gradually became nodular and was associated with a mildly painful swollen joint. He gradually developed swellings over the proximal interphalangeal joints of many fingers of both hands, chiefly on the dorsum but also anteriorly (Fig. 1, p. 45). During this period he described " bumps " which came and went over the dorsum of the extensor surface of the forearm at the elbow. Five years before he was seen, thickening of the palms had begun, with gradual extension into the fingers on the medial side of the palm (Fig. 2, p. 45). Recently he had developed a nodular swelling over the right infra-patellar area.

During this period there were periodical regressions and recurrence of these infiltrations and swellings for variable periods, with eventual increased extension. He also had generalized aches and pains in the shoulders, knees, wrists and feet. These were not associated with swelling, redness, or increased joint temperatures. The pains were dull, worse in the morning or after excessive activity. Movement of the joints caused only slight increase in the pain. Periodically there were pains and swelling of the elbows with some restricted motion. A year and a half before he was seen, following a bout of biliary obstruction with jaundice, a cholecystectomy was performed. The jaundice remained for almost a month, and during this period he had complete relief from joint pains and stiffness with marked recession of the finger nodules. Several months later the swellings and symptoms recurred. Before hospitalization, following heavy physical effort, he developed severe pains in the shoulders, ankles, and knees.

Examination.—The patient was a well-developed white male, rather distressed and apprehensive. There was a small non-tender nodule over the sixth cervical spine. The shoulders were slightly painful on movement. There was tenderness above and below

the elbows with some limitation of movement, but no swelling or raised temperature. A small nodule freely movable under the skin was noted over the dorsum of the left elbow. The palms of both hands were wet and cold. There was dense infiltration of both palmar spaces over the medial half of the palm with extension to the bases of both little fingers. The overlying skin was partially free and dense. There were no contractures, and movement was unimpaired.

There were non-tender, firm nodulations varying from 0·5 to 4 cm. over the proximal interphalangeal joints of most fingers, anteriorly and posteriorly, as well as over the distal interphalangeal joint of the left middle finger. Similar nodulations were felt over the anterior surface of the proximal phalanges of both hands. These nodulations were not attached to the skin but appeared to be attached to the structures over the joint. They moved readily, and there was no limitation of joint movement. One similar nodule was felt over the right infra-patellar surface. The other joints were normal. The blood pressure was 130·80 mm. Hg. The heart and lungs were normal. The patient was afebrile.

Laboratory Findings.—Urine analysis was normal. The sedimentation rate was 5 mm. in one hour (Westergren); Urea nitrogen was 10 mg. per 100 ml.; uric acid 4 mg.; cholesterol 200 mg.; serum proteins 7·5 g., with albumin 4·9 and globulin 2·6; blood sugar 100 mg. per 100 ml. The Wassermann reaction was negative, cephalin-cholesterol flocculation one plus in twenty-four hours; basal metabolic rate —6. The white blood count was 9,700 with a normal differential count; haemoglobin was 97 per cent. with 4,900,000 red blood cells. The electrocardiogram was normal.

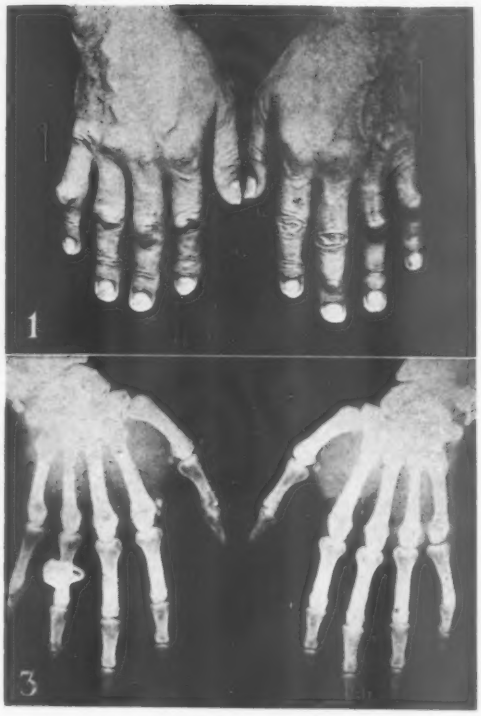
Radiographs.—The chest, skull, and elbows were normal. There was roughening of the greater tuberosity of the right humerus. In the area of the left sub-acromial bursa and under the outer left clavicle there were calcified densities approximately 1·5 cm. wide.

Both hands revealed normal joint spaces. Soft tissue nodulations were noted about the involved joints (Fig. 3, opposite). There were some osteo-arthritic changes about the terminal interphalangeal joints.

The knee joints were not narrowed. There was calcification of the right tibial plateau, and the lateral femoral margins with a spur on the left side.

Course.—During hospitalization he had marked relief of symptoms under a regime of rest in bed, sedation, and physiotherapy. A biopsy of the nodule of the left ring finger over the dorsum of the proximal interphalangeal joint was performed. At operation the nodule appeared as a firm, grey structure which was not attached to skin, but was adherent to the underlying tendon over the joint. It cut with some difficulty. The pathological report was of tendonous tissue showing increased interstitial collagenous material. There was some increased vascularity and a few foci of " round-cell " aggregates containing some cells with vesicular nuclei and pale abundant cytoplasm.

Following discharge on Nov. 22, 1948, the patient was placed on a basic regime of salicylates, physiotherapy, sedation, and, because of symptoms suggesting the climacteric, testosterone proprionate, 25 mg. intramuscularly twice weekly and 20 mg. orally daily. This was continued for a period of six weeks, and with this regime there was almost complete disappearance of all symptoms, including increased movement of the elbows. The nodule over the left elbow disappeared completely. During this period there was marked recession, but no complete disappearance of the nodulations over the fingers. On Jan. 18, 1949, following a psychic upset, he had recurrence of pains in all his joints and the size of the nodulations of the fingers increased. He also developed a new nodulation over the dorsum of the terminal interphalangeal joint of the left thumb, and nodules over the dorsum of the right elbow and the left infra-patellar area. His condition continued thus for several weeks. He refused to allow biopsy of the gastrocnemius muscle and the subcutaneous nodule.



FIGS 1 and 3.

FIG. 2.

Discussion

This case is one of nodular polytendovaginitis probably due to a "rheumatic state", most likely related to rheumatoid arthritis. The subcutaneous nodules, and the disappearance of symptoms during a bout of jaundice, serve further to classify the condition as rheumatoid arthritis.

Tendon-sheath involvement is a well-known finding in rheumatoid arthritis. This varies from simple serous tendovaginitis to chronic isolated or multiple nodular tendonitis. However, involvement of tendon sheaths alone without chronic joint disturbances is rare and serves further to confuse the various clinical pictures of rheumatoid arthritis (Bywaters, 1949); it is a manifestation of the systemic nature of this type of arthritis, with tendonitis assuming dominance.

As far as could be determined there was no intra-articular involvement in this case. There were no signs of synovial swelling, tenderness, or thickening. The nodulations appeared unrelated to any synovial structures, and were primarily related to the tendon tissues. Radiographs failed to reveal any evidence of joint or synovial reaction. Biopsies of joints were not undertaken, and due to the absence of clinical signs of synovial distention, aspiration of synovial fluid was not considered. Furthermore, during the course of the illness there were no complaints of redness or swelling of the involved joints.

Baumgartner (1946) recently reported two cases of "polytendonitis rheumatica". One case was associated with subcutaneous nodules and carditis. The other case was that of a chronic polyarthritis with early tendon-sheath involvement which later gave way to joint manifestations. Biopsy in the first case showed chronic tendovaginitis. Baumgartner stressed the point that tendonitis may assume dominance in the rheumatic syndrome, and he reviewed the literature on this subject, stressing the rarity of this clinical entity.

Roseno (1925) reported two cases of rheumatic tendovaginitis characterized by multiple tendonitis of a serous nature. He claimed a cure by the use of salicylates. Other case reports describe the onset of tendovaginitis, later replaced by arthritis, as an early phase of Still's disease or chronic polyarthritis.

In this author's opinion all these case reports represent various clinical stages of rheumatoid arthritis. This may vary from a pure tendon-sheath involvement, as in the case reported here, through all transitional forms to polyarthritis. Naturally the two may occur together, as evidenced by the occurrence of tendonitis, both acute and chronic, in the course of rheumatoid arthritis with multiple joint involvement. Nodular tendonitis may run a variable course, from an acute stage to a chronic proliferative phase, characterized by exacerbations and remissions as in the case reported here. It is possible that the cases reported by Roseno are an acute phase with a pathological picture of a serous inflammation. The nodular phase is a late proliferative stage with a pathological picture of a chronic tendovaginitis.

Pathologically this condition is related to that seen in rheumatoid arthritis with the basic involvement in tendon tissue instead of the synovia. In rheumatoid arthritis the basic pathology in the synovial membrane reveals hypertrophy of the endothelial lining and stroma, increased vascularity, follicle-like collections of round cells, and pannus formation. Here there are many of the same basic pathological alterations, with follicle-like collections of lymph-cells, mild inflammatory reaction, and increased interstitial collagenous material. However, the changes are definitely in tendon tissue and lack the other characteristics of synovial reaction.

The differential diagnosis of this condition should not be difficult in most cases. Inflammatory lesions of the tendons, such as tuberculosis, lues, and gonorrhoea, offer definite clinical pictures and courses. De Quervain's tendonitis and other traumatic conditions are usually single lesions and offer little difficulty. Tumours, especially xanthoma, may sometimes cause confusion, but the general picture and biopsies will distinguish them. The knuckle pads originally described by Garrod in 1893 and more recently by Parkes-Weber (1938), Jonsson (1949), and others may be the most difficult condition to differentiate. Knuckle pads are uncommon, occurring in the same locations over the extensor surfaces of the proximal interphalangeal joint, but omitting the thumb. They develop slowly and are symptomatic due to mechanical effects only. They frequently have a hyperkeratotic surface and move freely over the joint, but are attached to the overlying skin. The condition is also associated with Dupuytren's contracture. Histologically, they are like true fibroma. It can be seen from this description that differentiation may be almost impossible except by histological examination and by the clinical course.

In the case here reported it is felt that many features serve to substantiate the diagnosis of nodular tendonitis. The histological picture of tendonitis; the recurring subcutaneous nodules; involvement of the thumb, the distal interphalangeal joints, and the anterior surface of the fingers; attachment to joints and freedom of attachment to skin; and remissions with jaundice and therapy; these are some of the features which place this case in the rheumatic group.

Even more important than differential diagnosis is understanding of the

pathogenesis of the condition. This must be considered in the diagnosis of rheumatoid arthritis as one of the clinical manifestations of the systemic nature of the condition, with tendon-sheath involvement assuming dominance. Furthermore it must be remembered that at any point in the chronicity of the condition joint involvement may appear and may assume dominance.

Summary

A case of rheumatic polytendovaginitis is reported and the rarity of the condition is stressed. Its relationship to rheumatoid arthritis is shown; it is thought to be one phase of the systemic disease, with tendon-sheath involvement assuming dominance. Differential diagnosis is discussed, particularly with reference to knuckle pads, which very closely resemble the appearance of the fingers in this condition.

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Poly-teno-synovite Rhumatismale

RÉSUMÉ

On relate un cas de poly-téno-synovite et on souligne la rareté de cette affection. On montre son rapport avec l'arthrite rhumatismale; on croit qu'il s'agit d'une phase de la maladie générale où l'atteinte de la gaine tendineuse prend la place prépondérante.

On discute le diagnostic différentiel, particulièrement en ce qui concerne les bourrelets articulaires qui donnent aux doigts l'apparence rhumatismale.

Politenosinovitis Reumática

RESUMEN

Se relata un caso de politenosinovitis y se subraya lo raro de esta condición. Se muestra su relación con la artritis reumatoide; se piensa que se trata de una fase de la enfermedad general en que el envolvimiento de la vaina tendinosa ocupa el lugar preponderante.

Se discute el diagnóstico diferencial, particularamente en lo que se refiere a los nudillos entumecidos que dan a los dedos la apariencia reumatoide.

TENDON LESIONS IN RHEUMATOID ARTHRITIS
A CLINICO-PATHOLOGICAL STUDY

BY

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In his treatise on the nature and cure of rheumatism, Scudamore (1827) described the tendons as " knotty at their insertions and often contracted "; and Stockman (1904) used the term " tendinous rheumatism ". Klinge (1933) described microscopic lesions in the tendons and joint capsules of patients dying of active rheumatic heart disease, but the typical rheumatoid tendon lesions have been adequately described only by Scandinavian workers.

Helweg (1924) stated that snapping fingers were very common in patients suffering from rheumatoid arthritis. He noticed that in such cases large nodules could be felt in the palm of the hand, and that these nodules moved with the long flexor tendons of the fingers to which they were presumably attached. Sandberg (1941) reported a case of rheumatoid arthritis with snapping of all ten digits of both hands. At operation large glassy nodules were found in the long flexor tendons at the level of the metacarpo-phalangeal joints. Both Kahlmeter (1933) and Edström (1945) have stressed the importance of " tendinitis " as a cause of disability in rheumatic subjects, and in a survey of the Lund material Edström found clinical evidence of " tendinitis " and " peritendinitis " in 48 per cent. of 391 cases of chronic rheumatic polyarthritis. The long flexors of the fingers were the tendons most often involved, being affected in 38 per cent. of Edström's cases.

There is a large surgical literature on the subject of the snapping finger. In recent reviews (Compère, 1933; Henri, 1947) and in other important reports (Marchesi, 1905) the snapping finger or thumb was usually an isolated lesion associated with trauma, tumours, or occupational hazards such as piano playing; generalized rheumatic disease being exceptional in these cases. Most authors consider stenosis of the tendon sheaths to be an important cause of snapping, though nodules in the tendons also play their part. True stenosing tendovaginitis, as described by De Quervain (1895) and more recent writers, Finkelstein (1930) and Henri (1947), seems to be a rather different condition, being largely confined to the region of the radial styloid and being characterized by massive thickening of the fibrous sheath.

We have recently made a study of the tendon lesions of rheumatoid arthritis, and have compared them with a few cases of isolated snapping digits and of De Quervain's disease.

Clinical Material

During the past eighteen months we have explored the long flexor tendons of the fingers in fifteen cases of rheumatoid arthritis and in two cases that presented isolated snapping digits. In some of these cases advanced tendon lesions were

TABLE

INCIDENCE IN RHEUMATOID ARTHRITIS

Cases	Authors'	Edström's
With tendon lesions	42	188
Without tendon lesions	58	203
Total cases	100	391*
Sites of tendon lesions:		
Arms: Flexors only	31	125
Extensors only	0	26
Both flexors and extensors ..	6	12
Legs: Flexors only	2	24
Extensors only	2	12
Both flexors and extensors ..	3	4

* Edström's figures include both "tendinitis" and "peritendinitis".

known to be present and the operation was done as a therapeutic procedure, while in others the operation was done as a biopsy in early cases judged to have only minimal lesions; the following account of the pathological anatomy and clinical manifestation of the rheumatoid tendon lesion is largely based on this operative material.

We have also made a systematic clinical study of the incidence of these tendon lesions in rheumatoid arthritis, and the Table shows our findings in the last 100 cases seen in this department, together with Edström's figures for comparison.

Tendon lesions were judged to be present in forty-two of these patients, and in 37 of them the tendons of the long flexors of the fingers were affected. Other tendons affected were the extensors of the fingers, the tendons around the ankle joint, and the Achilles tendon. Our findings therefore agree with those of Edström and require no further comment.

In most cases of rheumatoid arthritis the tendon lesions are only one aspect of a generalized process involving the joints, muscles, and occasionally the viscera. But in rare cases the tendon lesions may be the chief cause of disability. The long flexors of the fingers are the tendons usually affected in these cases, and we will therefore describe in some detail the anatomico-pathological changes in these tendons and the disability which they produce, as a clear understanding of the clinical picture is essential for the proper care of these patients. These tendon lesions also provide an excellent opportunity for studying the histological changes which are found in the fibrous tissue in active rheumatoid arthritis.

Anatomico-Pathological Considerations

The long flexor tendons enter the palm by passing under the volar carpal ligament, at which level they are surrounded by the palmar synovial sheath. In the distal half of the palm the synovial sheath is lacking, each tendon being covered

merely by a thin fibrous sheath which contains three well-developed transverse bands (Fig. 1, B, B, B). In dissections of normal hands we have found that the most proximal of these bands is formed by the transverse fibres in the distal border of the palmar fascia. The middle band arises from the deep transverse palmar ligament and encircles the tendon at the level of the metacarpal heads. The distal transverse band lies in the fibrous sheath that binds the tendon to the volar aspect of the proximal phalanx (Fig. 1, S). Between these encircling bands the fibrous sheath is thin and lax.

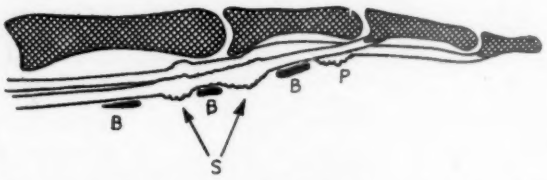

FIG. 1.—Diagram showing the sites of the nodule formation on the flexor sublimis tendon (S) and the profundus tendon (P). The three thick transverse bands in the fibrous sheath are marked (B).

In rheumatoid arthritis pathological changes may be found in both the tendons and their sheaths. The least change appears to be a dulling of the surface of the tendon. At a more advanced stage there is a thickening of the tendon, which looks yellow and streaked with grey gelatinous material. Frequently the tendon is nodular, and in extreme cases large cauliflower-like masses may be found (Figs 2 and 3). The nodules may lie in the centre of the tendon or on its surface, and some of the surface nodules look as if they had burst out from the centre of the tendon. In some severe cases the nodules become adherent to the tendon sheaths (Fig. 4). The nodules may be soft and gelatinous or firm and rubbery, and occasionally they may be quite hard.

These tendon changes are usually found in the palm at the level of the metacarpal heads, the tendons of flexor digitorum sublimis being more often affected than those of profundus. The index and medius are more commonly affected than the other fingers, and the thumb is but rarely involved. Occasionally one finds a large nodule in the profundus tendon just after it has come forward between the two heads of sublimis at the level of the proximal phalanx (Fig. 1, P), but nodules in other situations on the flexor tendons are uncommon.

The transverse fibrous bands in the tendon sheaths may soften and disintegrate, in which case the thickening and nodulation of the tendons causes little disability. But if the transverse bands remain intact, the thickened tendons become jammed under these bands, so interfering with active flexion of the fingers. Small nodules give rise to snapping fingers, and large nodules become completely impacted between two transverse bands so that all active flexion of the interphalangeal joints is lost.

The synovial sheaths in the palm and fingers usually contain a slight excess of fluid and there may be some proliferation and engorgement of the synovial tissue, but these changes are slight compared with the striking nodulation and swelling of the tendons themselves.

Clinical Picture

In those rare cases in which the tendon lesions are the sole cause of disability in the hand, the patients may complain of snapping fingers, but more frequently

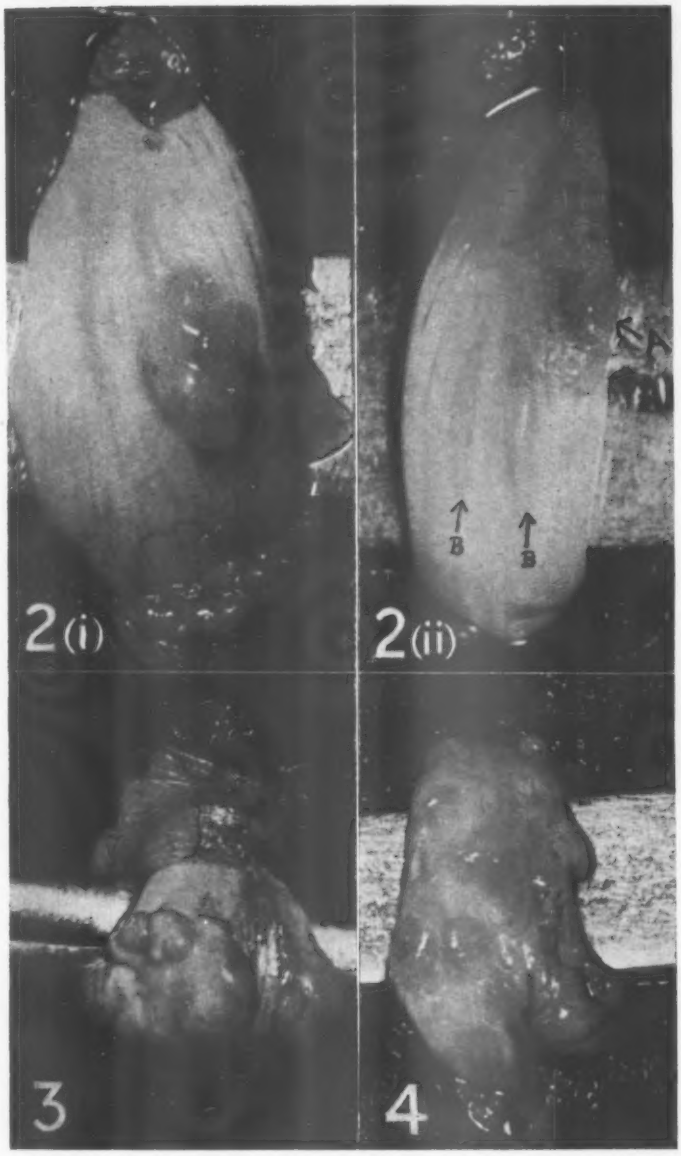

FIG. 2.—Operative exposure of flexor sublimis tendons in palm, showing (i) a typical tendon nodule and (ii) less severe changes, such as a small nodule at (A) and ridges of similar tissue at (B). The patient, a man 36 years old, had suffered from a low-grade rheumatoid process for 12 years. Joint changes were not severe, but he had multiple large necrobiotic nodules and enlargement of the spleen and lymph glands. The blood sedimentation rate was 30 mm. Westergren. After operation, hand function was greatly improved.

FIG. 4.—Operative exposure of flexor sublimis tendon in the palm, showing advanced replacement of tendon with nodular tissue. The adherent tendon sheath has been dissected off the tendon. All flexor tendons of both hands were affected. This patient, a woman 54 years old had suffered from rheumatoid arthritis for 6 years. There were severe arthritic changes in most of the joints and the disease was active at the time of operation. The blood sedimentation rate was 80 mm. Westergren. After the operation hand function was, if anything, worse.

FIG. 3.—Operative exposure of large firm nodule in flexor profundus tendon opposite proximal phalanx of index finger. The patient, a man 37 years old, had suffered for 3 years from typical rheumatoid arthritis, in clinical remission at the time of operation. The blood sedimentation rate was 18 mm. Westergren. This nodule was impacted, and operation was required to restore active flexion of the index finger.

the complaint is simply of weak and painful fingers. When asked to make a fist, the patients flex their metacarpo-phalangeal joints, but leave the interphalangeal joints fully extended. The interphalangeal joints can, however, be moved passively and painlessly through a full range and the joints themselves are not tender.

Palpation of the palm reveals firm, tender swellings in the region of the flexor tendons at the level of the metacarpal heads, and these swellings may be felt to move with the tendons as the fingers are passively flexed and extended.

Some patients are able to work their fingers loose during the day so that the full picture is only present in the early morning; but, though some active flexion may be regained, this movement usually has a snapping element and is at best extremely weak and painful. Because of the weakness and loss of flexion of the fingers, these patients are unable to hold objects such as tools and cooking utensils and have difficulty in opening doors; above all the women are unable to sew or peel potatoes, which is a serious handicap to many of these patients who are forced to lead a sedentary life because of their disease. In the majority of patients, however, the tendon lesions are accompanied by varying degrees of arthritis in the joints of the hands, the tendon lesions being relatively unimportant, and in these cases there may be some difficulty in deciding what proportion, if any, of the disability is attributable to the tendon lesions.

Treatment

The majority of rheumatoid tendon lesions require no special treatment. In the early acute cases the tendon thickening subsides as the disease process remits, and full movement may be regained. In severe cases the fibrous sheaths soften as the disease progresses and full movement may be restored in spite of massive nodule formation.

When pain is a prominent feature, relief may be obtained by a volar plaster slab which supports the hand in the position of rest with the wrist in extension and the fingers in partial flexion, though this should be removed once a day for gentle exercises. Helweg recommends massage and Edström uses *x*-ray therapy to hasten resolution in these cases, but we have not found it necessary to use either of these forms of treatment.

The important cases are those which fail to regain active movement of the fingers although the disease process is relatively quiescent as judged by good general condition, low sedimentation rate, and absence of active arthritis. These patients often present massive nodulation of the tendons as well as large nodules elsewhere in the body, and these cases, we think, may be usefully treated by operative incision of the tendon sheaths and such paring of nodules as seems expedient.

The operation is conveniently done under local anaesthesia. The tendons are exposed by a transverse incision in the creases of the palm and finger according to the site of the lesion.* The tendon sheaths are then slit open; with a little burrowing the incision in the tendon sheath can be carried well up into the finger so that all three constricting bands are divided. Both the sublimis and the profundus tendons are then hooked up and any obvious nodules removed until the tendons move quite freely. Only the skin is sutured, and the incision is protected by a plaster cast with a volar slab extending to the middle

* In some cases incisions were made along the length of the tendon to facilitate exposure for photography.

of the basal phalanx, so immobilizing the metacarpo-phalangeal joints and helping to break the patient's habit of flexing the finger at this joint only. Active flexion of the interphalangeal joints is started at once, and in a favourable case without concomitant arthritis a good grip can be regained in three to four weeks.

Postoperative Results

Seventeen patients have been operated on in this way. In nine the operation was planned as a therapeutic procedure and the results have been fairly satisfactory in that increased movement and a stronger grip have been maintained for periods of three months to one year. In eight patients the operation was essentially exploratory. One of these patients, who had very active disease and much concomitant arthritis, is worse, but the remainder are if anything slightly improved though the result would not have warranted an operation as a purely therapeutic procedure. We therefore suggest that the value of operative treatment may be worth exploring in a few carefully selected cases in which the disease process is not very active; but the long-term results are as yet unknown, and in at least one of our cases there has been a recurrence of snapping. On the other hand, if any operative reconstruction of the rheumatoid hand is being considered, the proportion of the disability due to tendon lesions must be carefully assessed, as any attack on the joints may prove fruitless if the chief cause of disability is in the tendons.

One of the interesting features of these tendon lesions is the opportunity they provide for studying the microscopic changes which occur in fibrous tissue during the early and active stages of rheumatoid arthritis.

Histological Findings

Previous histological studies of rheumatoid arthritis have been largely confined to synovial membrane, muscle, and subcutaneous tissue, although Klinge (1933) mentioned inflammatory lesions occurring in the tendinous structures around joints. But the only histological description we have found of the typical rheumatoid tendon lesion is Lundquist's account of Sandberg's case (1941). This report is brief, stating that the tendon sheath was infiltrated with plasma cells and lymphocytes and showed fibroblastic proliferation and occasional fibrinoid degeneration; the tendons were described as being infiltrated in places with " chronic inflammatory altered " connective tissue. We will therefore describe the tendon and tendon sheath changes in some detail. For convenience the tendon and tendon sheath will be considered separately.

Material and Methods.—From the fifteen cases of rheumatoid arthritis subjected to operation, thirty-eight biopsies of the flexor tendons and fifteen biopsies of tendon sheath were taken for histological examination. For comparison we have examined tendons and tendon sheaths in five cases of De Quervain's disease. Paraffin sections were cut after fixation in either 10 per cent. formol saline, 4 per cent. lead acetate, or Carnoy's fluid. The stains used included toluidine blue, Haidenhain's azan, Mayer's haemalum and eosin, Weigert's elastic stain, and Van Giesons stain combination, Gomori's reticulin method, Lendrum's phloxine tartrazine, and Pollack's rapid trichrome method. Occasionally sections were stained for bacteria by the Gram and Ziehl-Neelsen stains. In a number of cases the biopsies were studied in serial section.

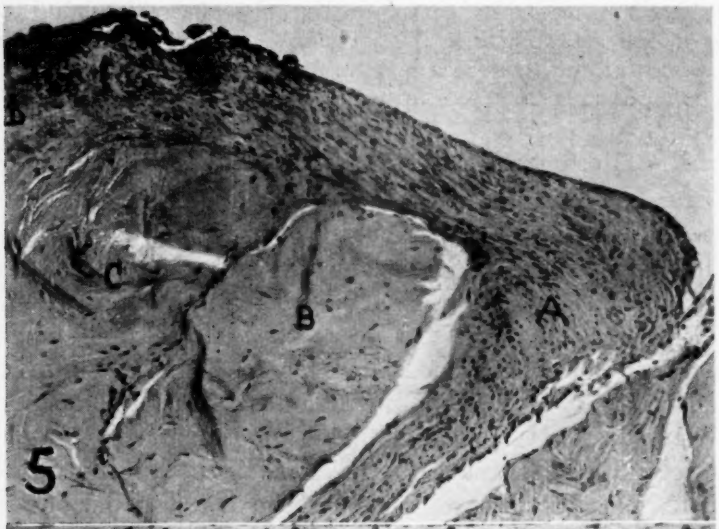

FIG. 5.—Fibrous thickening of the mesotenon (A). Normal mesotenon between healthy tendon bundles (B) and (C). At (D) the thickened mesotenon shows fibrinoid degeneration. Haemalum and eosin. ×75.

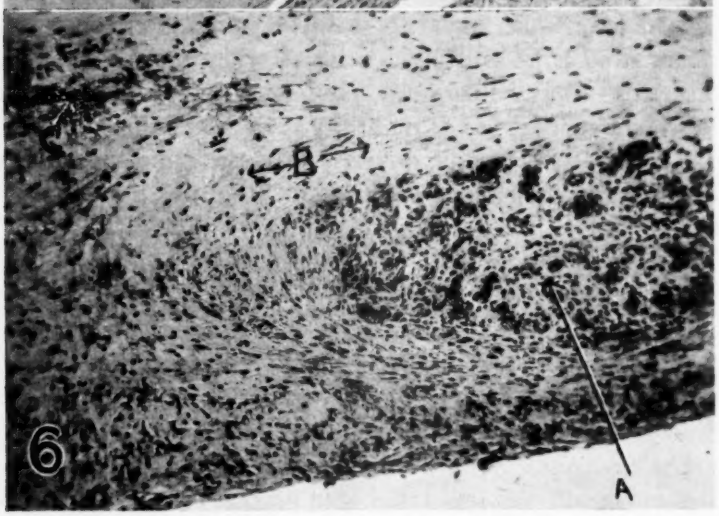

FIG. 6.—Grossly thickened peritenon showing characteristic congeries of young granulation tissue (A), areas of mature collagen (B), and a focus of fibrinoid degeneration (C). Haemalum and eosin. ×80.

Tendon.*—There were two cases in which at operation the only change noted was a dull streaky appearance of the surface. In one the changes were limited to the peritenon. This was thickened by old fibrosis, though the inner zone showed some oedematous loosening of the fibres and dilated capillaries, but no inflammatory infiltration. In the other case the findings in the peritenon were similar, except that the oedema was more marked. The mesotenon, however, was also thickened in parts, mainly by old fibrosis (Fig. 5, A), though in one region the tissue contained foci of fibrinoid necrosis (Fig. 5, D).

In two instances the tendon was found at operation to be grossly enlarged but not nodular. The pathological basis of this alteration was a widespread

* The loose connective tissue separating the tendon bundles will be designated "mesotenon". "Peritenon" refers to the loose connective tissue lying on the exterior of the tendon and binding the bundles together.

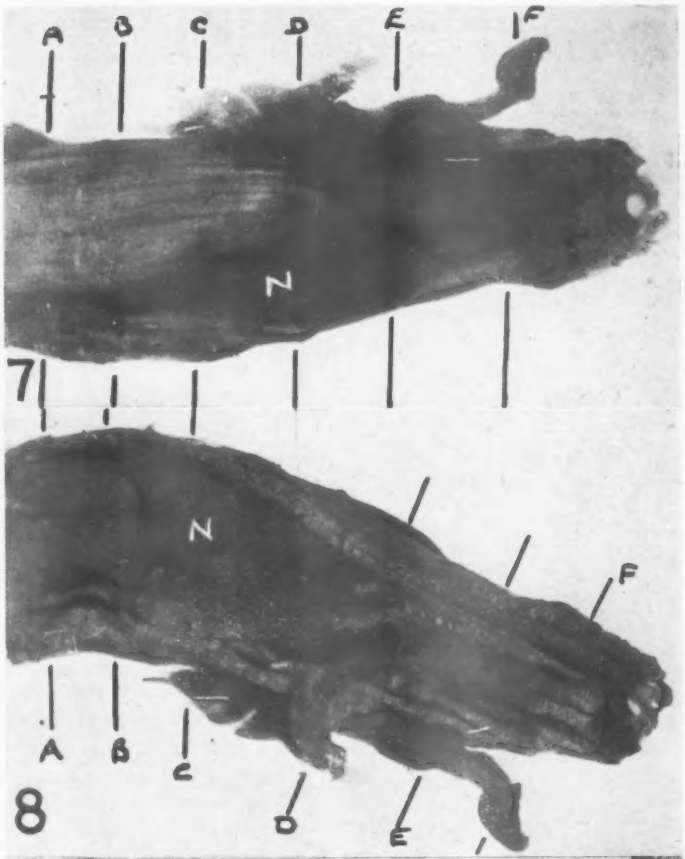

FIG. 7.—Superficial aspect of the biopsy taken from the tendon in Fig. 2. N = the surface nodule. The lines A to F in Figs 7 and 8 represent planes of section shown in Figs 9 to 14. ×4.

FIG. 8.—Deep aspect of the biopsy shown in Fig. 7. In the substance of the tendon there is a large nodule (N) well demarcated from the tendon bundles in parts, but merging with them in other places. ×4.

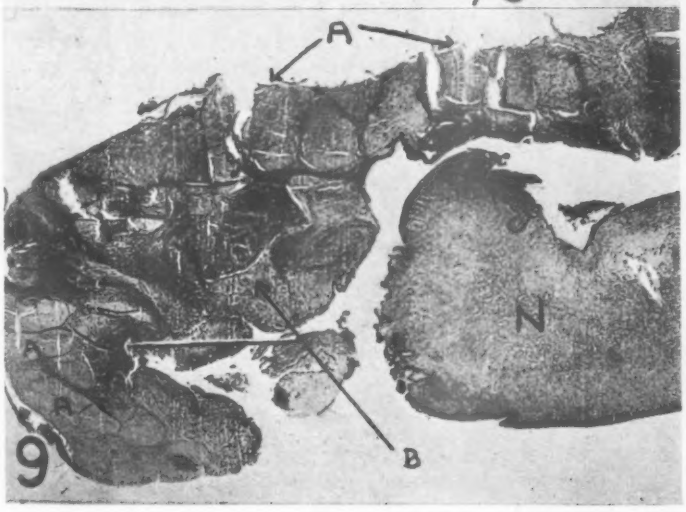

FIG. 9.—Section at Plane A in Figs 7 and 8. Many of the superficial tendon bundles are normal (A), but the deeper bundles are necrotic (B). Nodule (N) consists of a granular necrotic fibrinoid mass. Note absence of inflammatory reaction. Haemalum and eosin. ×20.

replacement of the peritenon and mesotenon by a thick layer of granulation tissue, a feature of which was the considerable histological variation found in neighbouring microscopic fields, especially in the more active parts. Areas of proliferating

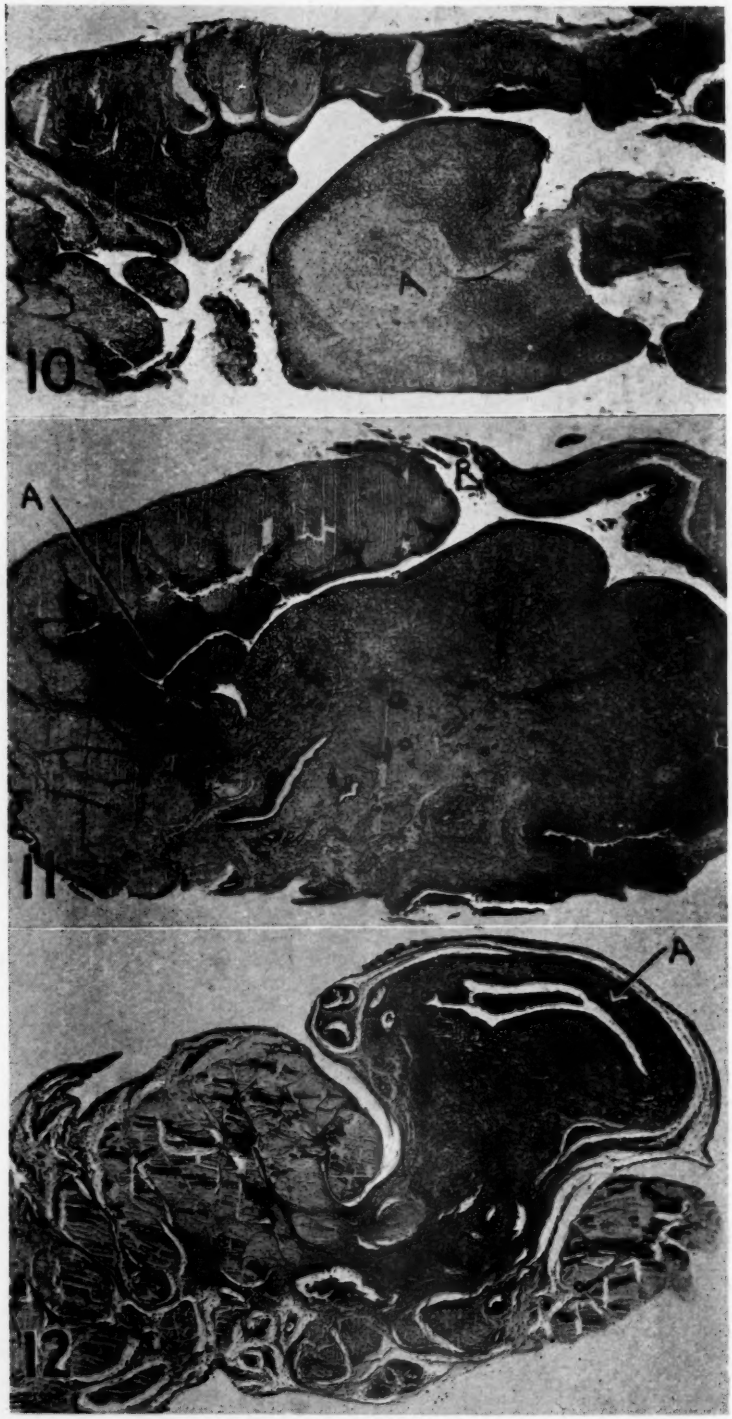

FIG. 10.—Section at Plane B in Figs 7 and 8. Changes are shown similar to those in Fig. 9, but in the centre of the necrotic nodule an area of proliferating capillaries and fibroblasts is present (A). Haemalum and eosin. ×20.

FIG. 11.—Section at Plane C in Figs 7 and 8. Necrotic nodule is largely replaced by granulation tissue which is separating the overlying tendon bundles and is about to break through the ruptured peritenon at (B). Necrosis of the deep tendon bundles is present at (A). Haemalum and eosin. ×20.

FIG. 12.—Section at Plane D in Figs 7 and 8 shows the surface nodule connected to deep tissue by a stalk. The upper part contains a typical necrobiotic focus with peripheral palisade (A). Haemalum and eosin. ×20.

capillaries and young fibroblasts, surrounded by a collar of fine connective tissue fibres, were scattered here and there (Fig. 6, A). Between these foci, fields of more

compact collagen and areas of fibrinoid necrosis were irregularly disposed (Fig. 6, B and C). Some scanty infiltration with polymorphs and lymphocytes was present. Apart from occasional small areas showing early degeneration, the tendon bundles were normal.

These changes showed no close resemblance to the Aschoff nodule, the subcutaneous necrobiotic nodule of rheumatoid arthritis, or the subcutaneous nodule of rheumatic fever (Bennett and others, 1940).

Thus in apparently less severe cases the lesions in the tendons were mainly found in the mesotenon and peritenon, in which thickening by granulation tissue or fibrosis was the dominant feature.

The majority of the tendon biopsies showing nodule formation were essentially similar, and their main pathological features may be illustrated by describing the findings in one fairly typical case.

At operation a medium-sized nodule (0·75 cm. by 0·5 cm.) was found on the surface of the flexor sublimis tendon of the middle finger (Figs 2 and 7). Naked-eye examination of the biopsy revealed another large nodule on its deep aspect (Fig. 8). The whole specimen was cut serially in transverse section, and the histology will be depicted by describing the changes noted in passing through the series from the plane A to the plane F, as indicated in Figs 7 and 8.

At the level A (Fig. 9), the nodule on the deep aspect consisted of a granular mass of fibrinoid necrotic material loosely attached to the overlying tendon bundles. Many of the latter, although still recognizable as such by virtue of the preservation of the general tendon bundle pattern, showed varying degrees of fibrinoid degeneration. The intervening mesotenon also showed fibrinoid necrosis and in some places was thus involved when the enclosed tendon bundle appeared normal. Only the most superficial part of the biopsy was entirely normal at this level. There was, hereabouts, a striking absence of inflammatory cellular infiltration or proliferative activity in relation to the necrotic and degenerative areas.

In the region B the picture was altered by the appearance in the interior of the necrotic nodule of a small area of proliferating capillaries and fibroblasts (Fig. 10). In succeeding sections this area of granulation tissue rapidly enlarged until it almost completely replaced the necrotic nodule and surrounding necrotic tendon bundles (Fig. 11). Although generally homogeneous, there was in places some lack of uniformity in this granulation tissue, areas of young fibroblasts and capillaries being intermingled with more mature collagen fibres and small foci of fibrinoid necrosis. As the region C was approached, the deep nodule of granulation tissue increased further in size and, pushing between the superficial tendon bundles, moved towards the surface (Fig. 11). At this point the peritenon was necrotic and ultimately ruptured (Fig. 11, B); and through this breach the enlarging nodule of granulation tissue emerged to appear on the superficial aspect of the tendon as a surface nodule (Fig. 12). The greater part of the circumference of this nodule was entirely free from the adjacent surface of the tendon, but its base remained attached to the interior of the tendon by a short stalk (Fig. 12). From the plane C (Fig. 11) to the end of the series the deep nodule was gradually replaced by normal tendon bundles. About the level D (Fig. 12) the structure of the superficial nodule presented an even more varied histological pattern than that previously noted in the granulation tissue in the deep part of the biopsy. Areas of fairly compact collagen occurred in juxtaposition with foci of capillaries and proliferating fibroblasts and areas of fibrinoid necrosis. In other places widely dilated capillaries were found embedded in fine fibrous tissue, and in still other areas numerous swollen fibroblast nuclei lying in an avascular

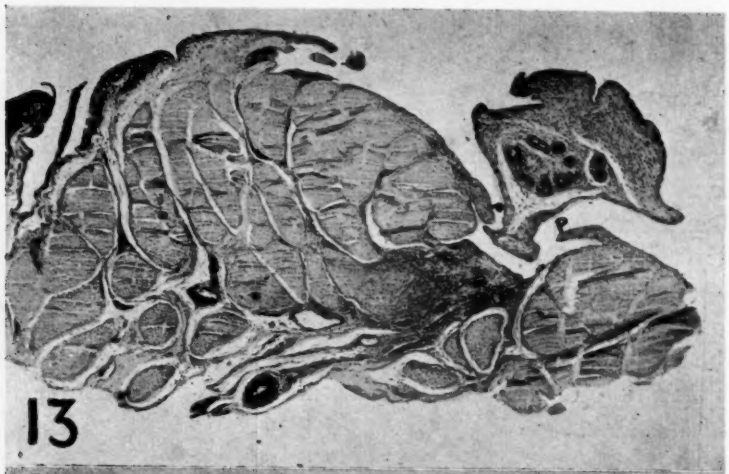

FIG. 13.—Section at Plane E in Figs 7 and 8. The surface nodule appears disconnected from the biopsy. At its base the free ends of the ruptured peritenon (P) can be seen. At this level the nodule consists largely of relatively mature fibrous tissue. Haemalum and eosin. ×20.

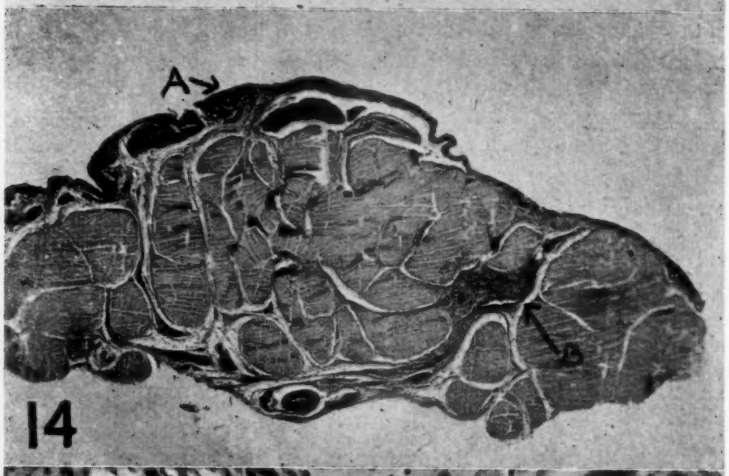

FIG. 14.—Section at Plane F in Figs 7 and 8. Note focal thickening of the peritenon (A) and increased vascularity of the tendon. At (B) there is some fibrous thickening of the mesotenon. Haemalum and eosin. ×20.

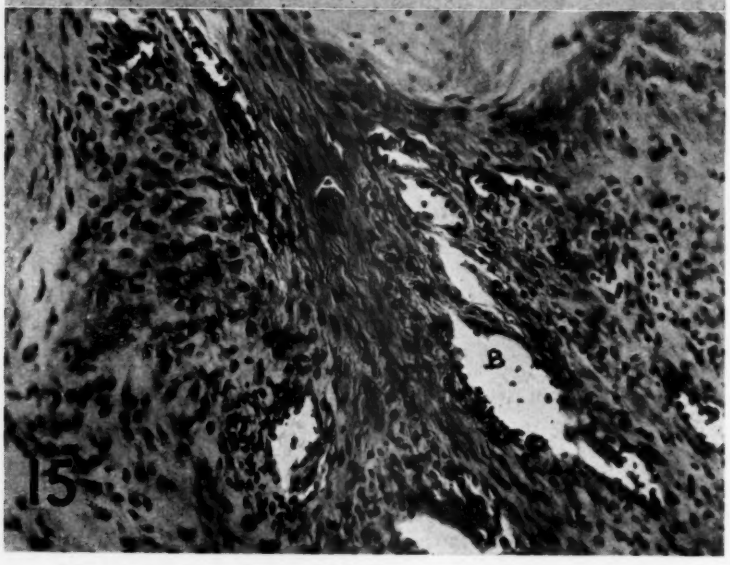

FIG. 15.—Part of the surface nodule in Fig. 12, showing degrees of maturation of the fibrous tissue: a stand of mature collagen (A); dilated capillaries (B); a group of swollen fibroblasts (C). Haemalum and eosin. ×140.

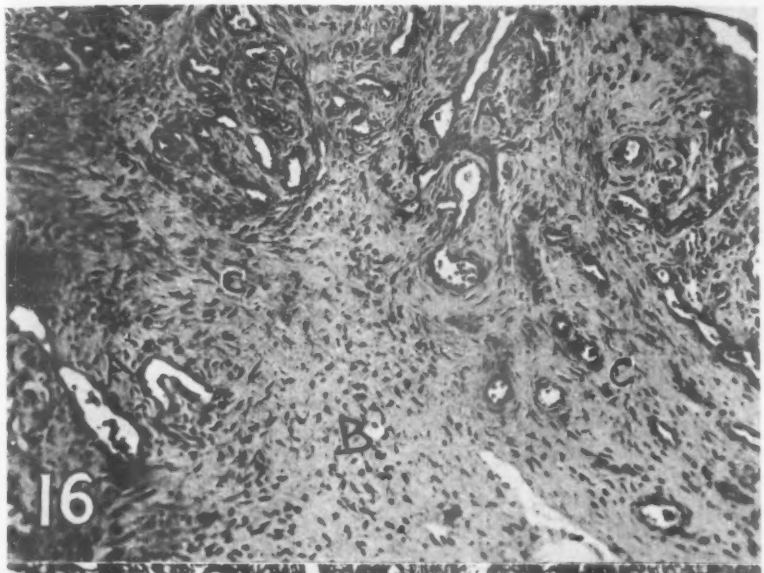

FIG. 16.—Part of a tendon nodule showing congeries of capillaries and fibroblasts (A), sparsely fibrous avascular area (B), and areas of mature collagen (C). Haemalum and eosin. ×95.

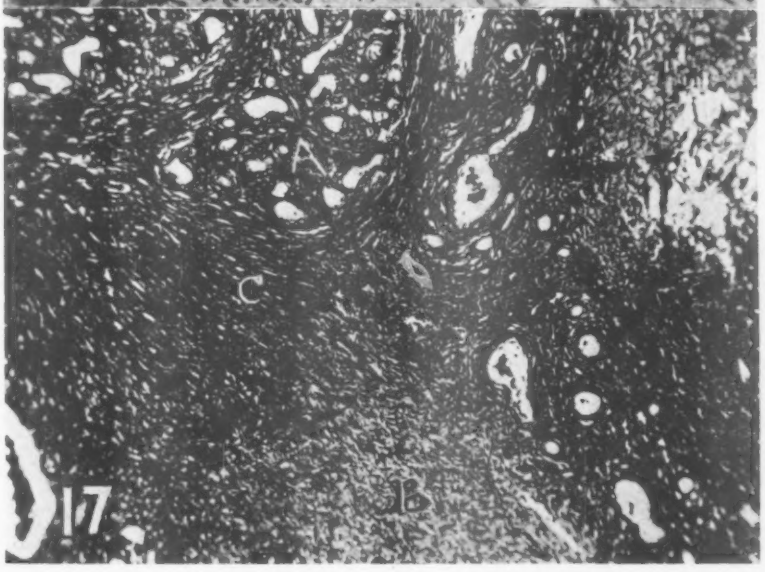

FIG. 17.—Consecutive section but one to that shown in Fig. 16, showing variations in fibre density. Gomori's reticulin method. ×95.

matrix predominated (Figs 15 and 16). Moreover, these various areas showed no regular orientation to each other, and their proportions varied in different parts of the nodule. Around some of the necrotic patches a palisade of connective tissue cells developed, the focus then being indistinguishable from the commonly occurring subcutaneous necrobiotic nodule (Fig. 12, A). Although polymorphs, lymphocytes, and plasma cells were present, especially in the vicinity of the necrotic foci and in areas of young granulation tissue, inflammatory infiltration was never a prominent feature in the nodule.

From the plane D to the end of the series there was a marked increase in the vascularity of the deeper parts of the tendon. At the level E (Fig. 13) the surface nodule appeared to be disconnected from the main part of the biopsy, though the point of its origin from the deeper parts of the tendon was still apparent from the rounded free ends of the ruptured peritenon. In this region (E) the nodule consisted mainly of relatively mature quiescent fibrous tissue.

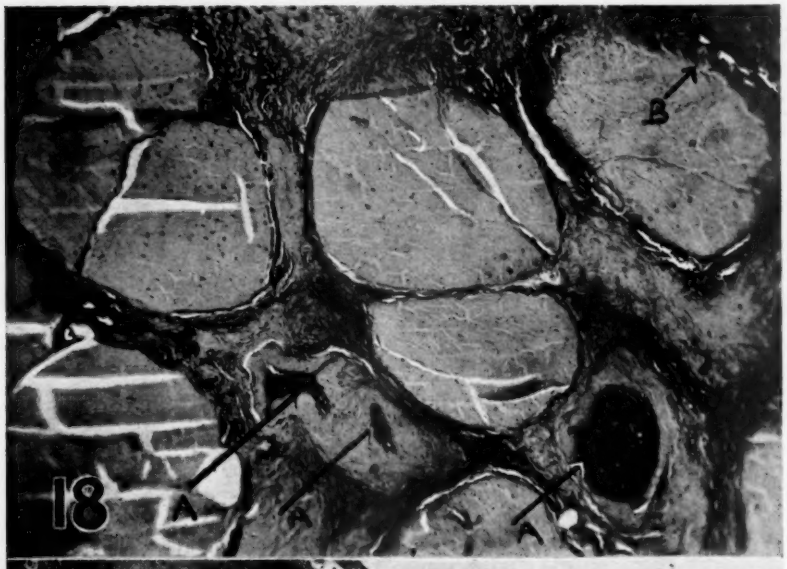

FIG. 18.—Focal necrosis in tendon bundles (A). At (B) the necrosis involves the periphery of the bundle. The mesotenon is irregularly thickened and shows fibrinoid necrosis at (C). Haemalum and eosin. ×75.

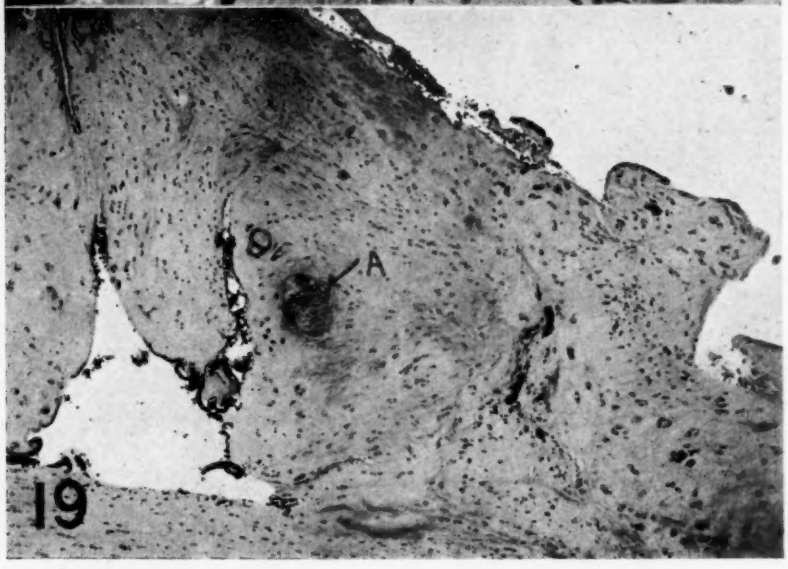

FIG. 19.—The base and part of a fibrocartilaginous type of tendon nodule with areas of mucoid degeneration (A). Haemalum and eosin. ×48.

In the remaining sections in the series the surface nodule gradually disappeared and normal tendon bundles occupied the deep parts of the biopsy. Finally the sections differed from normal tendon only in focal thickenings in the mesotenon and peritenon and some increase in vascularity (Fig. 14).

Some further remarks may serve to complete the above description of the changes occurring in this severe type of tendon lesion. From the nature of the material, casual sections can hardly be expected to reveal the findings described above. Further, when the biopsy consists only of the surface lesion (as happened in some of our cases), the complete picture of its pathogenesis will not be evident histologically. As in the case described above, surface nodules appear commonly to arise by the extension of granulation tissue originating in the deep parts of the tendon.

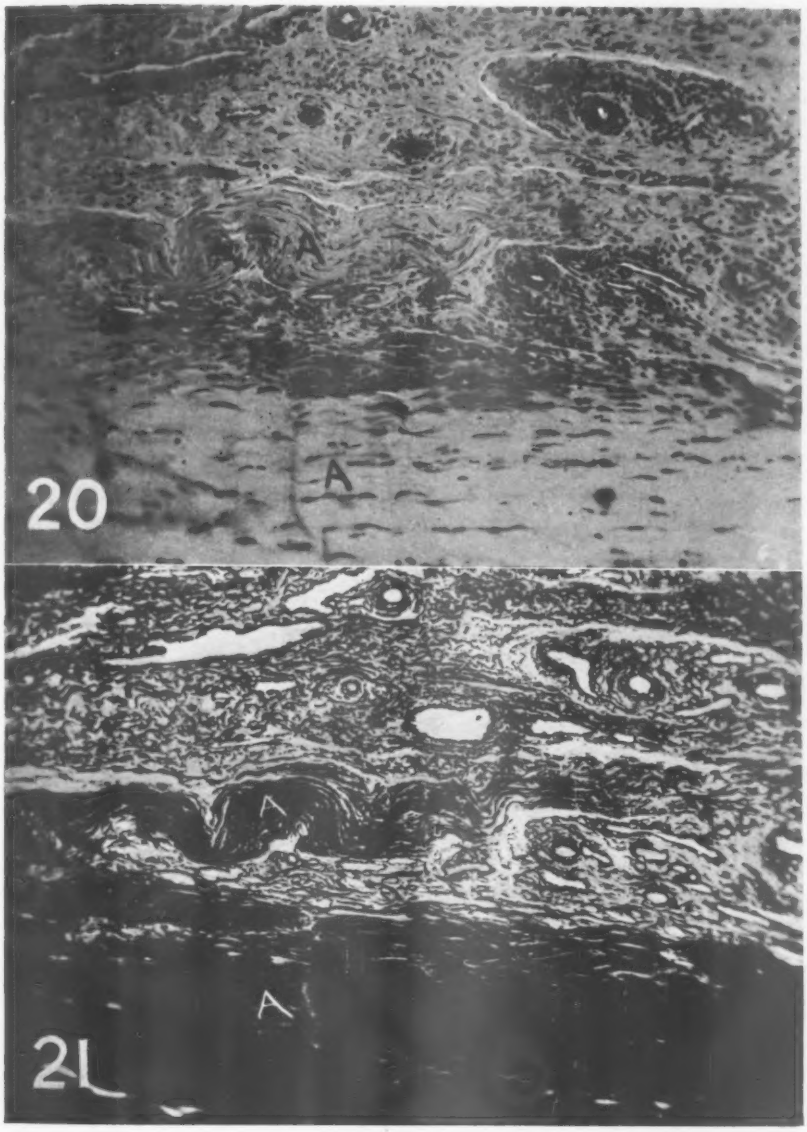

FIG. 20.—Shows part of a normal tendon bundle (A) disappearing into an area of granulation tissue. The difficulty here is to know whether normal tendon has changed so as to present the appearance of granulation tissue, or whether the latter is merely replacing an area of necrotic tendon. Haem-alum and eosin. ×75.

FIG. 21.—Consecutive section to that shown in Fig. 20, to illustrate the fibre pattern. Gomori's reticulin method. ×75.

Occasionally, however, small surface nodules may result from purely local connective tissue proliferations in the peritenon. Again, while massive tendon bundle necrosis was a feature in the case described, it was not uncommon to find merely a few fibres or part of a single bundle involved in the necrotizing process (Fig. 18).

In a few cases both superficial and deep nodules were made up mainly of old fibrous tissue containing some dilated capillaries and arterioles. But this quiescent form showed no close correlation with the clinical assessment of activity of the disease. Moreover, active and quiescent nodules were sometimes seen in one and the same patient.

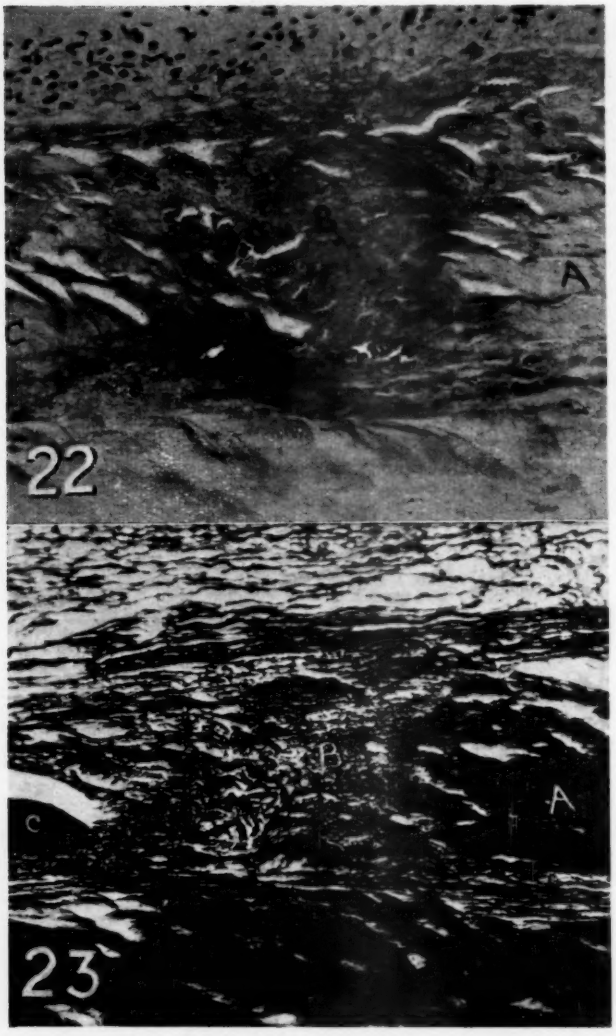

FIG. 22.—Early tendon fibre degeneration. Normal tendon (A) and (C) becomes indistinct at (B) where scattered polymorphs are present. Haemalum and eosin. ×110.

FIG. 23.—Consecutive section to that shown in Fig. 22. Note the altered fibre pattern in the area of degeneration. Gomori's reticulin method. ×110.

There was, however, one exceptionally hard nodule formed of almost completely avascular fibrocartilage containing small areas of mucoid degeneration (Fig. 19). The tendon bundles at the base of the nodule also showed a type of fibrocartilaginous change, though less marked and accompanied by considerable increase in vascularity. Clinically the patient had mild inactive rheumatoid arthritis and, although all intermediate stages between this and the common granulation tissue type of nodule were not seen, the suggestion may reasonably be made that the fibrocartilaginous nodule represents a possible end stage of the more usual surface lesion.

Tendon Sheath.—At the proximal and distal ends of the biopsy portions of the synovial sheaths of the palm and digit were usually seen. They commonly showed a chronic non-specific synovitis with lymphocytes and plasma cells infiltrating oedematous areas containing numerous dilated capillaries. In most cases the intervening fibrous sheath was either normal or showed minor changes, mainly consisting of small areas of oedema or fibrinoid necrosis associated with some capillary dilatation and slight inflammatory infiltration. Occasionally, however, areas of fibrinoid necrosis and granulation tissue were more extensive. When the surface layer of flattened cells was involved, deposits of fibrinoid material containing polymorphs were found.

The chronic synovitis may be merely secondary to the abnormal friction occasioned by the presence of nodules and enlargement of the tendon, for identical synovial sheath changes may be found at the limits of the thickened part of the sheath in De Quervain's disease, which is also characterized by abnormal movement

of the tendon in its sheath and which occurs mainly in non-rheumatic patients. Nevertheless, the average case of true stenosing tenosynovitis with its pronounced hyaline thickening of the sheath and minor tendon changes is easily distinguished both macroscopically and microscopically from the usual changes found in rheumatoid arthritis.

Early Tendon Changes.—In a number of biopsies we were able to study what appeared to be the early stages of tendon fibre degeneration. At first the compact fibrillar appearance of normal tendon became indistinct, or sometimes the fibres were regrouped into thick strands (Fig. 22). At this stage the fibres showed a tendency to stain blue after Mayer's haemalum and were often loosely infiltrated with polymorphs. After reticulin staining they were often fragmented and displayed a tendency to rupture and curl up on themselves (Fig. 23). As the typical fibrinoid appearance developed, the fibres often broke up into droplets. The tendon cells appeared first to enlarge and then to disappear. Occasionally degenerating fibres could be seen rejoining normal tendon. More often they disappeared into a reticulin network containing young fibroblasts and capillaries. Sometimes normal tendon fibres appeared to merge into a mass of granulation tissue, a finding which presented a fundamental difficulty in interpretation; for it was always uncertain whether the granulation tissue had merely replaced a necrotic area of tendon or whether the latter had degenerated in such a way as to produce a tissue with histological features resembling maturing granulation tissue (Figs 20 and 21).

Summary and Discussion of the Histological Findings.—The digital flexor tendons consist almost entirely of collagen fibres and ground substance. For this reason they are a particularly useful site in which to study the collagen changes in rheumatoid arthritis. In the main, our findings are in general agreement with what has already been deduced about these changes from studies in other sites such as the subcutaneous tissue. We will, therefore, draw attention here only to those of our findings which seem to be of particular interest.

In the tendon the essential lesion is often microscopic in dimension and almost always irregular in distribution ; and even in a single section individual lesions of varying severity and age may be encountered. The degree of alteration varies from an oedematous separation of the fibres to a reduction of the compact tendon fibre system into a swollen homogeneous granular mass containing at first a reticulin network, but later becoming completely afibrillar. In adjacent mesotenon or peritenon there is a pronounced formation of granulation tissue ; and the tendon nodule, the commonest cause of tendon disability, is an expression of the exuberant production of this tissue in the active stages of the disease.

Not infrequently, nodules occurring on the surface of the tendon can be regarded as a mass of granulation tissue isolated from parent connective tissue. And, since lesions identical with the subcutaneous necrobiotic focus of rheumatoid arthritis may occur in such nodules, it would seem that at least one form of genesis of this structure is a focal fibrinoid degeneration of performed nonspecific granulation tissue.

There is, in fact, much evidence in our material suggesting not only that parent

collagen (tendon bundle, peritenon and mesotenon) may be involved by fibrinoid necrosis, but that the associated granulation tissue may, at any stage in its development, also undergo similar degenerative changes. Thus, the usual course of maturation of this tissue is interrupted here and there by the occasional and irregular appearance in it of focal areas of degeneration; and these foci appear to act as stimuli for the further production of young granulation tissue. Such a sequence of events provides an explanation for the large amounts of granulation tissue produced; it may also explain the characteristic irregularity of the general histological pattern and the diversity in age and density of the collagen fibres found in this tissue (Fig. 17).

That this character of the granulation tissue in the active stages of rheumatoid arthritis is not limited to the tendon lesion is, perhaps, evidenced by the massive accumulations of pannus that may occur in the joints in this disease. But apart from this special feature the cellular tissue response is essentially non-specific—at least in the sense that an approach to diagnosis is possible only when the typical necrobiotic focus with characteristic palisade occurs, which is by no means a constant finding.

There was, nevertheless, ample opportunity to study the necrobiotic focus, especially the process by which it enlarges. This would appear to depend upon a necrosis of part of the peripheral palisade, which is promptly followed by the formation of a new palisade layer, and so on. The area of necrosis in the palisade layer occurs irregularly, first at one point, then at another, thereby accounting for the peculiar and characteristic serpiginous outline of the lesion. A similar account was given by Bennett and others (1940) of the subcutaneous necrobiotic focus. This finding also provides another example of the liability of the repair tissue to undergo focal fibrinoid necrosis with the resulting production of more granulation tissue.

The general problem of repair in tendon, particularly following trauma, was reviewed by Albertini (1929). It may, however, be stated that in the opinion of many workers the process is a form of replacement fibrosis, the basis of which is a connective-tissue proliferation in the mesotenon and peritenon. In our material granulation tissue not uncommonly appeared to be replacing necrotic tendon bundles. But the final stages of healing were not observed, and the ultimate process of repair of these tendon lesions remains an open question.

Summary

1. The clinical features of rheumatoid tendon lesions in the hand are described and the lesions are shown to occur in approximately half the cases of rheumatoid arthritis.

2. In fifteen cases the tendons were explored at operation, and this material was used for a study of the morbid anatomical changes in the tendon and tendon sheath.

3. Thirty-eight tendon biopsies and fifteen biopsies of the tendon sheath from these fifteen cases formed the basis of the histological study.

4. The histological findings in serial sections of one case are described in detail.

5. The mode of origin of the tendon nodule, the histological nature of the tissue reaction, and the early histological changes in the tendon fibres are described.

We wish to express our thanks to Professor S. L. Baker for his helpful criticism and for reading the manuscript.

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Lesions Tendineuses dans l'Arthrite Rhumatismale; étude Clinique et Anatomo-Pathologique

RÉSUMÉ

1. On décrit les traits cliniques des lésions rhumatismales tendineuses de la main et on montre qu'elles surviennent à peu près dans la moitié des cas d'arthrite rhumatismale.
2. Dans quinze cas les tendons furent examinés à l'opération et le matériel recueilli fut utilisé pour étudier les changes anatomiques morbides du tendon et de sa gaine.
3. Trent huit prélèvements du tendon et quinze prélèvements de la gaine tendineuse de ces 15 cas forment la base de cette étude histologique.
4. On décrit d'une façon détaillée les résultats histologiques de l'examen des séries de coupes dans un cas.
5. On relate le mode de formation du nodule tendineux, la nature histologique de la réaction tissulaire et les changes histologiques des fibres tendineuses au début.

Lesiones Tendinosas en la Artritis Reumatoide: Estudio Clinico-Patologico

RESUMEN

1. Se describe los caracteres clínicos de las lesiones tendinosas de la mano y se demuestra que estas lesiones ocurren aproximadamente en la mitad de los casos de artritis reumatoide.
2. En quince casos los tendones fueron explorados en el curso de una operación y el material así recogido fué empleado para estudiar las alteraciones anatomo-patológicas del tendón y de su vaina.
3. Treinta y ocho biopsias del tendón y quince biopsias de la vaina tendinosa de estos quince casos forman la base del estudio histológico.
4. Se describe detalladamente los resultados histológicos de una serie de cortes en un caso.
5. Se describe el modo de originar del nódulo tendinoso, la naturaleza histológica de la reacción del tejido y las alteraciones histológicas tempranas de las fibras tendinosas.

FIBROSITIS OF MUSCLES

BY

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Interest in the rheumatic diseases has much increased during the last ten or twelve years. Articular rheumatism has, however, received more attention than the non-articular forms, because the former may take a more dramatic course and often result in disablement.

Fibrositis is a term applied to several different kinds of rheumatism in the soft tissues; we are in doubt as to the cause of many of them, but we know that it is not a single illness. From a prognostic and therapeutic point of view it is very interesting and useful to try to differentiate the kind of rheumatism that may be hiding behind the name fibrositis.

Fibrositis from Overwork

In this paper I have tried to distinguish a form of fibrositis of the muscles caused by overwork, and have attempted to explain its appearance and why the empirical forms of treatment help. There is nothing remarkable in the fact that muscles are often affected through overwork, since they make up 43 per cent. of the weight of the body and have important functions in metabolism, in carriage, in walking, and in movements of all kinds. I have left out of consideration infectious diseases of the muscles that can be verified by microscopical demonstration of the presence of Aschoff's or Klinge's nodules, or of other symptoms of specific rheumatic disease. I have also left out of consideration nodular fibrositis at the tendinous insertions, and fatty herniations in the fascia. I have considered only tender fibrositis in the muscle—the German "Hartspann"—that may be recognized in overworked musculature by means of palpation.

When this condition is being investigated the technique of palpation is of great importance. The patient should be completely relaxed, and palpation should be done symmetrically, with the skin well greased so that friction is completely eliminated. Plenty of time should be taken: it is important not to hurry.

When a muscle is trained sufficiently slowly it will undergo hypertrophy, and, on account of an increase of the sarcoplasm, each cell will grow larger; the number of fibres will be more or less unchanged. When a muscle is working, the capacity of its capillaries increases, and by hard work it may increase up to fifty times its resting capacity. When in activity the muscle contracts and is altered in shape, compressing the capillaries which have to supply it with blood. Thus the afflux

is reduced, and instead of getting more blood the muscle will get less. If the contraction is prolonged for more than a certain time, it will thus work more or less anaerobically. In a working muscle there will always be a certain degree of ischaemia and also a certain number of fibres forced to work anaerobically.

Another reason why the muscles under certain circumstances work more or less anaerobically is that the pressure of the intramuscular tissue fluids increases by working. By hard work it may increase up to 200 or 300 mm. Hg; that is to say, it is higher than the systolic pressure and will consequently compress the capillaries.

The stronger the contraction, and the longer it continues, that is to say, when the work is chiefly static, the more do these circumstances assert themselves.

Under anaerobic working conditions glycogen is decomposed into lactic acid, which, on account of the ischaemia already mentioned, will remain where it is produced, that is, in the working muscle. By prolonged hyperfunction a change of consistency will appear here—not only during the period of restitution but also afterwards—this is what we in Denmark call " myosis ". This form of fibrositis can be verified by palpation; it is local and must not be mistaken for the more diffused increase in consistency which is due to acute simple *hypertrofia e labore.* In English it is often called " fibrositis of the muscles ", " myalgia " or, less correctly, "spasm"; in German it is "Myogelose" or " Hartspann ". The terms " spasm " and " Hartspann " involve stimulation, as distinct from the terms " fibrositis " and " Myogelose ", which express a change of consistency only.

By means of electromyography it is now possible to separate these conditions and to distinguish between a real " spasticity ", that is a relatively permanent stimulation of the muscle, and a mere change of consistency.

Buchtal's Work

According to Buchtal (1940), it is probable that the double refractive substance of the myofibrils consists of flexible chains of molecules, in which molecules or parts of molecules are mutually connected by fairly firm valences. When a muscle fibre is extended passively, the molecules assume a longitudinal orientation, returning to a less tense state when the exterior forces cease to exert an influence. In the equilibrial state these firmly connected chains of molecules lie almost completely folded up. In uninnervated resting fibre these molecule chains are not in their equilibrial state, but are more or less straightened out. Buchtal assumes that the forces causing this orientation are due to the presence of an electric field. In resting fibre the condition of molecular aggregates, the micellae, is thus determined by the result of certain elastic and electric forces and corresponds to arrangement of the molecules in a somewhat extended rubber cord. Buchtal's experiments were performed on frog-muscles, but were later confirmed by Høncke (1947) on warm-blooded musculature. According to Buchtal, it seems as if electron microscopy may open new working-hypotheses regarding the mode of action of high elastic substances, and so the picture shown in the diagram would be altered.

Explanation of Overwork-Fibrositis

The explanation of the kind of fibrositis here spoken of may be that the molecule-chains of the part of the muscle in question have joined—with increase in stiffness of the muscle—and the muscle-cell does not respond to the stimulation of the motor end-plates, this corresponding to the state of clinical fibrositis. The consistency of this fibrositis is pasty, viscous, and stiff, that is, in myosis the elastic qualities alter. The changed condition of this fibrositis will persist in general anaesthesia. It may be thought that the linked molecule-chains are due to insufficient regeneration of the stretching forces—electric or other—a fact which is due to oxidation or to an accumulation of metabolic products.

As mentioned before, some of the muscle fibres work anaerobically, owing to compression of the vessels with decreased supply of oxygen.

We cannot yet, in fixed specimens, distinguish between a contracted and an uncontracted muscle. There is, therefore, nothing remarkable in the fact that from a pathological-anatomical point of view no difference is found between a normal muscle and a muscle with altered qualities caused by hyperfunction. From a clinical point of view the acute form of this fibrositis is more bulky, pasty, inelastic, and sore, and the chronic form is more fibrous, firm, and atrophic, and less sore. Radiating pains can actually be caused by pressure on, or pull of, the fibrositic muscle, and this fact may sometimes cause confusion with "neuritis" and "neuralgia". Clinically one may distinguish between primary and secondary myosis, and this distinction may be of some value prognostically and therapeutically; but there is no real difference between the two forms of fibrositic muscle.

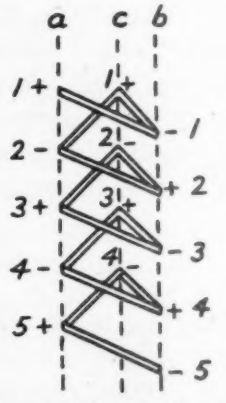

FIGURE.—Model of the minute structure of muscle fibres, according to Buchtal (1942, p. 13). "Spiral", with three series of charges (a, b, and c).

A secondary fibrositic muscle may appear as the immediate consequence of another disease. For example, spondylosis, prolapsed intervertebral disk, or tubercular spondylitis may cause protracted tension in the muscle; when this tension, or strain, has persisted for some time, it is replaced by a fibrositis. Similarly, as a result of cardiac disease, a fibrositic muscle may be caused by an axone-reflex in the muscles of the chest region. On account of unnatural walking, arthrosis coxae causes fibrositis in lumbar and gluteal muscles.

Primary fibrositis in a muscle is directly caused by too heavy external work; that is to say, the myosis will be the result of forced work without intervals for rest, or of hard unaccustomed work, either because the unaccustomed work is wrongly performed technically or, in the case of nervous people, because they are too strained during their work. The principal cause is thus hyperfunction with ischaemia, but predisposing factors may be neurotic conditions of any kind.

As mentioned above, the appearance of one of the forms of fibrositis of the muscles (myosis) may be due to overwork of the musculature, with a resulting decreased blood supply, deficiency in oxygen, and accumulation of metabolic products, and so we find a good explanation of the effects of the old empirical methods of treatment: rest, together with massage and thermotherapy.

Treatment

According to the above, treatment will be as follows.

Prophylaxis.—The best position in which to work at a convenient pace should be ascertained. Rest periods should be adequate and the work varied. The worker should be allotted to the work for which he is best fitted. Training in relaxation should be given, and psychic friction at the place of work should be avoided.

Therapy.—This should consist in rest. If necessary, different work should be found or the pace reduced. Massage should be given to increase the flow of blood and to remove accumulated metabolic products. (Massage is an art: you have to work " with your brain in your fingers ". Often for early myosis gentle treatment is needed, but myosis of longer standing may need stronger treatment.) Hot packs and short-wave therapy may also be given.

Injections of substances to dilate the circulation may be given (for example, 2-benzyl-4, 5-imidazoloinhydrochloride or for myosis of longer standing a dilute solution of formalin).

In secondary myosis the primary illness must be treated, a prolapsed disk by operation, or spondylosis by *x*-ray treatment or manipulation. Cardiac diseases need treatment of the heart, and flat feet need orthopaedic treatment.

During rest-activity, the state of reflex hyper-irritability (as revealed by electromyography) might be treated in different ways: (1) by increasing the blood-circulation in the muscle; (2) by decreasing the irritability of the motor end-plate by quinine orally or by injection, or by intravenous calcium; (3) by decreasing the irritability of the proprioceptic terminal organs, for example by injecting " novocaine " at the trunks or at the roots; (4) by decreasing central irritability or transmission through the synapsis by means of sedatives.

In the case of neurotic patients, training in relaxation is important for prophylactic as well as for therapeutic purposes.

Rehabilitation.—When the patient is free from pain, light gymnastic exercises should be started. Later, before the patient begins work, heavier exercises can be prescribed in order to strengthen the muscle as much as possible. The patient should go back to his former work slowly and with supervision of his working technique.

Conclusion

Rheumatism in the soft tissues is of great social importance. Physicians ought to take more interest in these diseases in order to avoid leaving such patients in the hands of the quacks.

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Fibrosite des Muscles

RÉSUMÉ

On expose l'importance du rhumatisme musculaire par rapport à celle du rhumatisme articulaire. On distingue entre le rhumatisme musculaire du au surmenage d'un muscle et les autres variétés. On relate son origine, sa base physiologique et ses symptômes. Cette maladie peut être différentiée au moyen de l'électromyographie des spasmes musculaires. On note la possibilité de la confusion avec la neuralgie et la névrite.

Le rhumatisme musculaire peut être reconnu par la palpation. On distingue des altérations musculaires (nommées " myoses ") primaires et secondaires. On expose des raisons pour lesquelles les vieilles méthodes empiriques de traitement réussissent.

Reumatismo Muscular

RESUMEN

Se expone la importancia del reumatismo muscular en relación con el reumatismo articular. Se distingue entre el reumatismo muscular debido a la fatiga de un musculo y otras variedades. Se relata su origen, su base fisiológica y sus síntomas. Esta enfermedad puede diferenciarse de los espasmos musculares por medio de la electromiografia. Se nota la posibilidad de confusión con la neuralgia y la neuritis.

El reumatismo muscular puede estar reconocido por medio de la palpación. Se distingue entre las alteraciones musculares (llamadas " miosas ") primarias y secundarias. Se expone las razones del éxito de los viejos métodos empíricos de tratamiento.

HEBERDEN SOCIETY

December Meeting.—The Annual General Meeting of the Heberden Society was held on Friday, December 9, 1949, at the Royal College of Surgeons of England with the President, Dr. W. S. C. Copeman, in the chair. The following officers and committee members for 1950 were elected:

President, Chairman, and Librarian:	Dr. W. S. C. Copeman.
President Elect :	Prof. Sir Henry Cohen.
Treasurer :	Dr. E. Fletcher.
Senior Hon. Secretary :	Dr. R. M. Mason.
Junior Hon. Secretary :	Dr. F. Dudley Hart.
Ordinary Members of the Executive Committee :	Dr. Hugh Burt.
	Dr. E. G. L. Bywaters.
	Mr. W. D. Coltart.
	Dr. G. D. Kersley.
	Dr. L. G. C. Pugh.
	Prof. R. E. Tunbridge.

The following were elected to Honorary Membership:

Dr. M. B. Ray, D.S.O., O.B.E.
Lord Webb-Johnson, K.C.V.O., C.B.E., D.S.O., T.D.
Prof. L. J. Witts, F.R.C.P.

The Chairmen of the Dominion Councils of the Empire Rheumatism Council were elected as Honorary Corresponding Members *ex officio*.

Prof. Wood Jones, F.R.S., then delivered the Heberden Oration* for 1949 on " Classical Gout ". He opened by explaining that the mere fact that he was the owner of a little private gout no more entitled him to speak as an authority on gout than the owner of, say, a David Cox had the right to pose as an authority on British water-colour pictures. He disclaimed, as an anatomist, all specialized knowledge of purine metabolism, although he was prepared to accept, with reservations, the traditional definition of gout as a disturbance of uric acid metabolism. He stipulated further that he was only going to deal with the natural history of the disease: he attacked the use of the term " gout " in an adjectival sense, since this word altogether destroyed the whole idea of the very real entity of the condition typified by podagra. He was glad to note that the more modern physicians were beginning to recognize other precipitating factors than those of gluttony and excess of drinking such as John Hunter had suggested! More was heard to-day of such factors as trauma, psychic influences, stresses and strains, and allergy. He went on to describe from personal experience the acute attack in the region of the metatarso-phalangeal joint of the big toe in graphic terms. He questioned,

* The Oration will be published in full in the *British Medical Journal*, 1950, 1, 561.

however, whether it was correct to consider the site of the lesion as strictly intra-articular. In support of this he demonstrated two radiographs—one of the foot of a man who had had attacks for 10 years, and one of his own big toe which had been the site of repeated attacks since 1913. Neither showed any changes of gout. He considered that it was more probable that the site was periarticular.

Sir Charles Scudamore had suggested in 1811 that vascular changes might be responsible for the sudden changes around the joint, and earlier still, in 1769, John Caverhill had made a similar suggestion.

Prof. Wood Jones next drew attention to the phenomenon of dryness of the skin in the affected region at some stage in the disease. There was, however, a third phenomenon less easily described—the pain. The great obstacle to describing a subjective sensation such as pain was that man, from earliest times, had used mechanistic terminology; thus there were no words adequate to describe our sensations, and this was readily observed in the classical descriptions of the pain of gout.

Discussing the mechanism of these phenomena he described the anatomy of the arteriovenous circulation associated with joints. In 1872, Höjer had demonstrated that a viscous fluid injected into the arteries would pass into the veins without going through the capillary bed, flowing through anastomoses between veins and arteries. He himself had recently tried the same experiment, using a thick solution of gelatine, coloured vermilion, injected into the popliteal artery. The material appeared within a few seconds returning via the popliteal vein. The specimen was demonstrated. Hare's Law stated that the further the arterial tree goes from the heart the more free are the anastomoses, and these, moreover, always occurred in the neighbourhood of joints; but what had never been properly recognized was the fact that accompanying the arterial anastomoses were much more ample and complex venous anastomoses, and that it was between these that short-circuits took place. Thus, every part of the limb becomes an independent circulatory system of itself. He suggested, therefore, that gout might be a vasomotor neurosis, allying it to erythromelalgia and other similar conditions. There were many similarities with causalgia too, and a rather striking dissimilarity from Raynaud's disease, gout being almost the negative of that phenomenon.

The Annual Dinner of the Society was held in the college on the same evening, 75 members and guests being present. Lord Webb-Johnson, Lord Lucas, and Professor Wood Jones, to whom Dr. W. S. C. Copeman presented the Heberden Medal for 1949, were the guests of the Society.

The following day, December 10, the meeting was continued in the Anatomy Theatre of St. Thomas's Hospital, when Prof. D. V. Davies read a paper on "Anatomical Aspects of the Rheumatic Diseases". He described two aspects of the anatomy of the joints—the vascular pattern and the nerve supply. With regard to the former, he gave a description of the relations of the vessels of the synovial joint to those of the tissues, including the bones. The bearing of these facts on some features of rheumatic diseases and the methods used in their treatment were considered, and Prof. Davies went on to discuss the role of nerve fibres in joint function and symptomatology.

Dr. W. A. Fell then read a paper on the nerve supply of the hip joint in which an attempt was made to correlate different types of referred pain with lesions in different parts of the capsule.

January Meeting.—A clinical meeting of the Heberden Society was held at 5 p.m. on January 6, 1950, in the Meyerstein Hall of Westminster Medical School, London. Sir Arnold Stott, K.B.E., welcomed the Society to its first meeting at Westminster on behalf of the Hospital and Medical School. Six cases were shown, of which five are detailed below.

Case 1. Osteoporosis and Eunuchoidism for Diagnosis (presented by Dr. Denis Irwin). A man now aged 28 had complained since August, 1948, of loss of strength, and pain of sudden onset and marked severity between the shoulders and around the ribs, which persisted until treatment was instituted ten months later. He had been married seven years but had no children. He did not shave until he was 24 and even now only shaved approximately once a week. There was no relevant family history. He had served in the R.A.F. during the war in the top medical category. Four previous fractures at various times due to trauma had healed normally. He had lost one and a half stones in weight during the last two years. The facies was immature and the skin relatively hairless. The lower jaw was prominent but there was no soft tissue hypertrophy of hands or feet. Teeth were normal. There was a moderate dorsal kyphosis. Axillary hair was normal, pubic hair of feminine distribution. The penis was normal in size but the testes underdeveloped. Tenderness was present over the spine and ribs. X-rays showed generalized decalcification of all bones with collapse of two upper dorsal and two lumbar vertebrae. There was mild spondylolisthesis and basilar invagination of the skull. The pituitary fossa was normal.

Biochemical findings were all normal repeatedly, including renal, thyroid, and liver function tests, and serum calcium, inorganic phosphates, and alkaline phosphatase. Faecal fats and sternal marrow were normal. Bence Jones proteose was absent. Wassermann reaction and Kahn test were negative.

Treatment consisted of large doses of calciferol. Excessive doses produced toxic effects, but resulted in dispersion of the symptoms and feeling of well being, with 12 lb. increase in weight during three months spent in hospital. After his discharge his wife became pregnant. Seven months after treatment was discontinued symptoms started to return. No diagnosis was made in this case.

In discussion Prof. L. S. P. Davidson suggested that a pituitary factor might well be present. Dr. Kellgren suggested that a bone biopsy might throw some light on the aetiology. Dr. Bywaters said that this was clearly a case of osteoporosis, not of osteomalacia, the fault lying not in the deposition of calcium but in a defect of the matrix. He suggested that 11-oxysteroid estimation might be helpful. Mr. Coltart and Professor Maclagan also spoke.

Case 2. Rheumatoid Arthritis in an old case of Graves's Disease with Lung Changes (presented by Dr. F. Dudley Hart). In 1928 the patient, now a man of 50, developed Graves's disease with exophthalmos. Deep *x*-ray treatment was instituted with entirely satisfactory results and there have been no toxic symptoms since 1932. About 1935 rheumatoid arthritis commenced. In 1941 symptoms exacerbated and at this time clubbing was first noticed by the patient in his fingers. There were no respiratory symptoms at this or any other time, nor have there ever been physical signs in the lungs. He was admitted to Westminster Hospital in 1948, under the care of Mr. E. P. Brockman, and it was then discovered by *x*-ray that he had fine fibrotic changes throughout both lung fields. Since that time the lung condition and clubbing have remained unchanged. In view of the

cases published by Dr. Philip Ellman and others, this case was shown as a possible case of rheumatoid disease of the lungs.

Dr. Ellman then showed radiographs of similar cases in his collection. Dr. Bywaters and Prof. L. S. P. Davidson also spoke.

Case 3. Acromegaly with Ankylosing Spondylitis (presented by Dr. Andrew Bogdanovitch). The symptom, first attributable to ankylosing spondylitis in this woman of 53 years of age, was the onset nineteen years before, of a recurrent dull ache in the lower spine, which was relieved by a course of deep *x*-ray therapy. Fifteen years ago acromegaly was diagnosed when her hands became enlarged, but the typical facies was not noted until six years later. The condition does not appear to have progressed since, though her dorsal kyphosis has become more marked in the last three years.

In addition to these clinical features her dorso-lumbar spine was immobile, and lateral neck-movements were limited. The chest expansion at the upper breast level was ¾ in., and corresponded with a vital capacity of 2,500 cc., or 71 per cent. of normal for her physique. The most striking radiological features were complete fusion of both sacro-iliac joints, and ligamentous calcification of the lumbar spine. The skull showed enlargement of the sella turcica and thinning of the posterior clinoid processes.

Laboratory investigations showed that the blood sedimentation rate was 33 mm. at the end of one hour (Wintrobe) and the blood count, Wassermann reaction, Kahn test and gonococcal complement fixation test were negative. The serum globulin was high at 3·14 g./100 cc. and coincided with a thymol turbidity test of six, thymol flocculation of 2+ and serum colloidal gold of 3+. The 24-hour urinary excretion of 17-ketosteroids was only 4·4 mg.

The case was discussed by Drs. Ellman, Hart, and Bywaters.

Case 4. Ankylosing Spondylitis with Spontaneous Pneumothorax (presented by Dr. F. Dudley Hart). This case was shown to illustrate certain respiratory features in the disease, particularly with regard to therapy. This patient's case history was reported in the Section of Medicine of the Royal Society of Medicine, November, 1949.

Case 5. Acute Lymphatic Leukaemia in a Child presenting as Rheumatoid Arthritis (presented by Dr. John Dean). The patient, a girl aged 5 years, was admitted to the Westminster Children's Hospital under Dr. N. O. Richards, on Nov. 1, 1948.

For two months previously she had suffered short periods of pain and swelling in both knees and one wrist. The only abnormality was a hot, swollen, and painful left knee; there was no glandular or visceral enlargement. Hb, 81 per cent.; white cells, 5,000 per c.mm. (polymorphs 24 per cent., lymphocytes 64 per cent., monocytes 8 per cent., eosinophils 4 per cent.). *X* ray of the knee showed some decalcification.

For six months there was intermittent painful swelling of knees, ankles, wrists, and finally of the left index finger. She ran a Pel-Ebstein type of temperature all this time, and then rather rapidly became pale, and the liver, spleen, and cervical glands became somewhat enlarged. Hb, 36 per cent.; white cells, 10,000 per c.mm. (polymorphs 15 per cent., lymphocytes 49 per cent., myelocytes 11 per cent., prolymphocytes 13 per cent., lymphoblasts 12 per cent.; iliac marrow smear, 48 per cent. blast cells (probably lymphoblasts). Radiographs showed periosteal reactions in femora, humeri, and fingers, and leukaemic infiltration of femora, tibiae, fingers, and skull.

Treatment consisted of aminopterin and transfusions. Anaemia and intermittent joint pains persisted. Peripheral blood in November, 1949, showed marked granulopenia but few primitive cells. The patient is alive at the moment of this report.

NEW YORK RHEUMATISM ASSOCIATION

October Meeting.—A Clinical Conference was held at the University Hospital, New York, on Wednesday, Oct. 19, 1949, under the chairmanship of James Tarsy. The programme consisted of the following papers:

Arrest of Rheumatoid Arthritis with Gold Salts: Orthopaedic Rehabilitation (Harry Bartfeld); An Unusual Case of Acute Arthritis with Skin Manifestations (Edward F. Hartung); A Case Illustrating the Management of Osteo-arthritis with Orthopaedic Supportive Measures (Harry Weiner); Two Cases Illustrating Corrective Measures in Rheumatoid Arthritis: (*a*) Treatment of Flexion Deformity of the Knee, (*b*) Treatment of Deformity of the Hands (Robert Preston).

January Meeting.—A joint meeting of the New York Rheumatism Association and the New York Academy of Medicine was held on January 5, 1950. Dr. Philip S. Hench, Head of the Department of Rheumatic Diseases, Mayo Clinic, and Professor of Medicine, University of Minnesota (Mayo Foundation), spoke on the " Endocrine Relationships to Rheumatoid Arthritis ".

Twenty-one cases of rheumatoid arthritis were treated with Compound E and adrenocorticotrophic hormone. Good results were obtained in all cases, but symptoms promptly returned when treatment was stopped. The dosage of Compound E was 100 mg. a day. When Compound E acetate was used, the initial dose was 300 mg. to start, then 100 mg. a day. Smaller doses (25-75 mg. a day) were ineffective. Sixteen patients were given short-term treatments of 8-66 days. Five patients received treatment for 4-9 months. Improvement was noted in articular and muscular function. Increased appetite, gain in weight, and euphoria were also noted. Laboratory evidence of improvement was evidenced by a drop in the erythrocyte sedimentation rate, and normalization of the blood proteins and blood count.

There were no definite signs of toxicity to Compound E or Compound E acetate. However, overdosage caused transient oedema, usually pretibial. Rounded facial contour, mild acne, hirsutism, and amenorrhoea were noted. Euphoria was later replaced by depression. The erythrocyte sedimentation rate slowly rose after an initial marked fall. Transient glycosuria and an altered glucose-tolerance curve were observed, but in no case was diabetes produced.

On a schedule of 100 mg. Compound E acetate a day, no changes were noted in the plasma bicarbonate, potassium, chloride, or sodium. On 200 mg. a day, an increase in plasma bicarbonate and a decrease in potassium and chloride were noted, no change in plasma sodium.

In rheumatic fever, Compound E and adrenocorticotrophic hormone were used with good results. In cases of rheumatic carditis, there was a prompt drop of

the erythrocyte sedimentation rate, change of the P-R interval to normal, and a drop in temperature and pulse rate. When treatment was given for five weeks and then discontinued, symptoms returned. A second course of treatment relieved the symptoms, which did not return after treatment was stopped the second time.

Initial work indicates that interrupted therapy may be better than continuous administration of the drugs. Compound F and not Compound E may be the true anti-rheumatic factor. When adrenocorticotrophic hormone is administered, Compound F and not Compound E can be recovered from the urine.

Experience with the use of oestrogen and testosterone is limited. However, they are of value in controlling the side effects of Compound E.

EMPIRE RHEUMATISM COUNCIL

The Lord Webb-Johnson has been elected a Vice-President, and Vice-Chairman of Council in place of Sir Walter Kinnear, who has retired on grounds of health.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

The recent International Congress of Rheumatic Diseases held in New York, at which Drs. Hench, Kendall, Slocumb, and Polley announced their discovery of the value of Cortisone in Rheumatoid Arthritis, emphasized the importance of these gatherings sponsored by the International League. Such congresses can only be attended by members of the League and in view of the stimulus to research in the subject given by this new work, the future congresses of the European League in Barcelona in 1951 (last week in May) and of the whole International League in Zurich in 1953, promise to be most important meetings.

Membership of the British Branch of the European League against Rheumatism is open to any doctor interested in the rheumatic diseases on payment of an annual subscription, which is used to defray the British League's subscription to the International League to meet Secretarial and other running expenses and to accumulate a small fund against the day when Great Britain will again become the host for an International meeting.

History.—The Ligue Internationale contre le Rhumatisme was founded in 1929 to act as a co-ordinating body for the International campaign against rheumatism. There had been previous attempts to form such a League, but there had always been difficulty in exchanging information because the same nomenclature has not been used in different countries to describe the various types of rheumatic diseases. Dr. Van Breemen of Amsterdam and Dr. Fortescue Fox of London took the leadership in the formation of the Ligue. But for World War I it would have been started earlier, for in 1913 a proposal was passed to study the rheumatic diseases more methodically in different countries, and a report was to have been given in St. Petersburg in 1917.

In 1925, at a meeting of the International Society of Medical Hydrology in Switzerland, an " International Committee on Rheumatism " was formed which later developed into Le Ligue Internationale contre le Rhumatisme, and in 1929 the first congress of the Ligue was held in Budapest. A medical journal, the *Acta Rheumatologica*, was started as a medium for the exchange of information and was only " liquidated " after the German invasion of Holland, where it was published. Subsequent congresses were held in Paris and Prague. In 1939 a congress was to have been held in New York, but this had to be postponed for ten years as during World War II all activities of the Ligue were suspended. The records were hidden from the Germans when they occupied Amsterdam, have survived and were shown at the congress held in New York in June, 1949.

Officers.—At the recent congress in New York the following Officers were elected:

President:	Prof. EJNAR JARLØV, Copenhagen, Denmark.
President-Elect:	Dr. ROBERT STECHER, Cleveland, Ohio, U.S.A.
Assistant to President:	Mr. O. DE BORNEMANN, Copenhagen, Denmark.
Secretary-Treasurer:	Dr. W. TEGNER, London, England.

Councillors of the Ligue Internationale

Dr. A. MICHEZ (Belgium).
Dr. E. JARLØV (Denmark).
Dr. W. S. C. COPEMAN (England).
Dr. M.-PIERRE WEIL (France).
Dr. A. DE CHATEL (Hungary).
Dr. H. W. LUNBERHUIZEN (Holland).
Dr. P. BARCELO (Spain).
Dr. F. SUNDELIN (Sweden).
Dr. K. M. WALTHARD (Switzerland).
Dr. A. LENNOCH (Czechoslovakia).
Dr. C. H. TRAEGER (U.S.A.).
Dr. OTTO STEINBROCKER (U.S.A.).
Dr. E. HARTUNG (U.S.A.).
Dr. E. BOLAND (U.S.A.).
Dr. CHARLES SLOCUMB (U.S.A.).
Dr. RICHARD T. SMITH (U.S.A.).
Dr. A. RUIZ-MORENO (Argentina).
Dr. F. HERRERA RAMOS (Uruguay).
Dr. L. M. SAENZ (Peru).
Dr. WALLACE GRAHAM (Canada).

PAN AMERICAN LEAGUE

President: Dr. ROBERT STECHER (U.S.A.).
Secretary: Dr. A. RUIZ-MORENO (Argentina).

EUROPEAN LEAGUE AGAINST RHEUMATISM

President: Dr. W. S. C. COPEMAN, *O.B.E.* (England).
Secretary: Dr. G. EDSTRÖM, Department of Rheumatology, Medical Division, University of Lund, Sweden.

BRITISH BRANCH OF THE EUROPEAN LEAGUE AGAINST RHEUMATISM

President: Dr. W. S. C. COPEMAN, *O.B.E., M.D., F.R.C.P.*
Treasurer: Dr. G. D. KERSLEY, *T.D., M.D., F.R.C.P.*, 6 The Circus, Bath (to whom subscriptions should be sent).
Secretary: Dr. OSWALD SAVAGE, *O.B.E., M.R.C.P.*
Executive Committee: Dr. W. S. TEGNER, *M.D., M.R.C.P.*
Dr. B. S. SCHLESINGER, *O.B.E., M.D., F.R.C.P.*

Clinics.—The following heads of clinics have been approached and have intimated that members of the League will be welcome. Prior notification of attendance should be given.

JUVENILE RHEUMATISM

Children's Heart Hospital, Woodlands Way, Wickham, Kent.
Thursday, 10.30 a.m., Dr. R. E. Bonham-Carter (by arrangement).

Canadian Red Cross Memorial Hospital, Maidenhead, Berks.
Dr. E. G. L. Bywaters (by arrangement).

Children's Heart Home, Lancing, Sussex.
Dr. D. de L. McCarthy (by arrangement).

ADULT RHEUMATISM

BATH

Royal National Hospital for Rheumatic Diseases.
Monday, 10 a.m., In-Patients, Dr. G. D. Kersley; Out-Patients, Dr. L. C. Hill.
Tuesday, 2 p.m., Out-Patients, Dr. J. B. Bennett.
Wednesday, 10 a.m., Out-Patients, Dr. P. W. McKeag.
Thursday, 9.30 a.m., Out-Patients, Dr. G. D. Kersley.

S.W. and Oxford Regional Rheumatism Research Centre.
Daily. Dr. G. D. Kersley.

BRISTOL

Royal Infirmary.
Friday, 10 a.m., Out-Patients, Dr. G. D. Kersley.

DROITWICH

St. Andrew's Brine Baths.
Tuesday, 9.30 a.m., Dr. J. W. T. Patterson.
Friday, 2 p.m., Dr. H. L. Milles.

HARROGATE

Royal Bath Hospital.
Monday, 10 a.m., Dr. Reah; 2 p.m., Dr. Rutherford.
Tuesday, 10 a.m., Dr. Potter; 2 p.m., Dr. Yeoman.
Wednesday, 10 a.m., Dr. Yeoman; 2 p.m., Dr. Rutherford.
Thursday, 10 a.m., Professor Hartfall.
Friday, 10 a.m., Dr. Wesley-Smith; 2 p.m., Dr. Reah.

LONDON

*Arthur Stanley Institute for Rheumatic Diseases, Middlesex Hospital, Peto Place, Marylebone Road, N.W.*1.
Monday, 2.15 p.m., Dr. Oswald Savage.
Tuesday, 10 a.m., Dr. Doris Baker; 2 p.m., Dr. R. Stone; 5 p.m., Dr. H. F. Turney.
Wednesday, 10 a.m., Dr. F. Howitt; 2.15 p.m., Dr. W. S. C. Copeman.
Thursday, 10 a.m., Dr. R. Stone; 5 p.m., Dr. W. S. Tegner.
Friday, 10 a.m., Dr. Ernest Fletcher; 5.30 p.m., Dr. Doris Baker.

*Post-Graduate Medical School, Ducane Road, Hammersmith, W.*12.
Tuesday, 2 p.m., Out-Patients, Dr. E. G. L. Bywaters.

*London Hospital, Department of Physical Medicine, E.*1.
Thursday, 10 a.m., Dr. W. S. Tegner.
Friday, 10 a.m.

*Royal Free Hospital, Gray's Inn Road, W.C.*1.
Wednesday, 1.30 p.m., Dr. Ernest Fletcher.

St. Stephen's Hospital, 369 *Fulham Road, S.W.*10.
Tuesday, 11.30 a.m., In-Patients, Dr. Philip Ellman.
Wednesday, 10 a.m., Out-Patients, Dr. Philip Ellman.
Thursday, 9.30 a.m., In-Patients, Dr. Francis Bach.
Friday, 9.30 a.m., Out-Patients, Dr. Francis Bach.

*West London Hospital, Hammersmith, W.*6.
Wednesday, 10.30 a.m., Dr. W. S. C. Copeman, Dr. Oswald Savage.

*Westminster Hospital, S.W.*1.
Wednesday, 2 p.m., Dr. F. Dudley Hart.

*University College Hospital, Department of Physical Medicine, Gower Street, W.C.*1.
Tuesday, 10 a.m., Dr. Hugh Burt.
Thursday, 2 p.m.

MANCHESTER

Nuffield Rheumatism Research Centre, Royal Infirmary, Manchester, 13.
Monday, 1.30 p.m., Out-Patients, Dr. J. H. Kellgren.
Wednesday, 10 a.m., In-Patients.

WORCESTER

Royal Infirmary.

Wednesday, 9 a.m., Dr. J. W. T. Patterson.

EDINBURGH

Northern General Hospital, Ferry Road.

Monday, 2 p.m., Dr. J. J. R. Duthie.
Wednesday, 2 p.m. (follow up).

Royal Infirmary.

Tuesday, 9.30 a.m., Dr. J. J. R. Duthie.
Friday, 2 p.m. (follow up).

GLASGOW

Royal Infirmary, 106 *Castle Street, Glasgow, C.*4.

Tuesday, 9.30 a.m., Dr. J. P. Currie.

Courses.—The following post-graduate courses have been arranged:

(1) March 25-26, 1950. St. Stephen's Hospital, 369 Fulham Road, S.W.10. Particulars through the Fellowship of Medicine.
(2) April 28-30, 1950. Empire Rheumatism Council Spring Week-End Course at the Apothecaries Hall, E.C.4. Particulars from the Empire Rheumatism Council.

Heberden Society Meetings.—Members of the British Branch of the League are invited to the following meetings of the Heberden Society:

(1) The Heberden Round on May 20, 1950, at the Hôpital Cochin, Paris, by Professor Coste, who has extended his personal invitation. The members of the French Branch are also to be invited.
(2) The General Meeting in London on Saturday, December 9, 1950 at 10.15 a.m., at the Meyerstein Theatre, Medical School, Westminster Hospital, Horseferry Road, S.W.1. Discussion on "Endocrine Aspects of the Rheumatic Diseases", by Prof. E. C. Dodds, F.R.S., and Dr. Peter Bishop.

Prior notification of attendance should be sent to The Secretary, Heberden Society, c/o Empire Rheumatism Council, Tavistock House (N), Tavistock Square, W.C.1.

BOOK REVIEWS

Further Rare Diseases and Debatable Subjects. By F. Parkes Weber. 1949. London: Staples Press. Pp. 236. 25*s*.

The value of the detailed study and publication of single rare and atypical cases is frequently under debate. There is no doubt of their great interest and that sometimes " the exception may prove the rule ", but publication of such cases in specialist journals has to be strictly limited. Dr. Parkes Weber has " from time immemorial " been widely regarded as the Specialist in Rare Diseases and in his new book he goes so far as to advocate the need for such a speciality. In 1946 he produced his first book of 165 pages on rare diseases in which he discussed cases of scleroderma and dermatomyositis, cholesterol degeneration in rheumatoid nodules, calcinosis, and acroparaesthesia with Heberden's node formation, subjects of particular value to those interested in rheumatism. He has now written a further volume on the same lines, describing more cases and in some chapters a follow-up of cases described in the first book. In his chapter on " Zest in Old Age " he gives his own reaction to recreation, as diagnosed by Sir James Paget, that to some " change of work is better than rest or amusing games ".

Of particular interest to Rheumatologists in this volume are the following chapters. " Necrobiotic Nodules in Rheumatoid Arthritis ", previously published in this Journal (1948, **1**, 63), describes the widespread nature of such nodules in the pleura, pericardium and myocardium and also cholesterol degeneration in certain cases, work substantiated by the post mortem findings on Case 12 and in Case 13 of an article also published in this Journal (Kersley and others (1946), **5**, 141). His case of calcinosis is of special interest in view of its debatable relationship to the collagen diseases. In this connection an interesting paper was read by Lansbury in Philadelphia, during the 1949 post-convention tour, suggesting a link between this disease and the calcinosis produced in guinea pigs as the result of deficiency of green vegetables. A crude cortical extract appeared to be of some value in treatment.

A useful review on panniculitis by Dr. Alice Carleton is included under the heading of Weber-Christian disease or relapsing febrile nodular non-suppurative panniculitis.

There is also an intriguing description of a case of idiopathic osteoporosis at the early age of 44, which is compared with Burrows and Graham's case, published in this Journal (1947, **3**, 129).

This book, though a rather unco-ordinated collection of papers on rare syndromes, only too often named after some author of lesser or greater distinction, who first described them, makes interesting reading. Unfortunately, there is often no suggestion why such a syndrome occurs or how it should be treated. There

are few readers who will fail to find in this book some case report which bears on their own particular interests in medicine, and all will pay a tribute of admiration to the wide knowledge and clinical acumen of the author. G. D. KERSLEY.

Rheumatism. By H. Warren Crowe, D.M.(Oxon), B.Ch., M.R.C.S., L.R.C.P. 1949. London: Staples Press Ltd. Second edition. Pp. 270. 17*s.* 6*d.*

The name of H. Warren Crowe has been associated with " Rheumatism " for many years, and despite the changing fashions of therapy, he has remained constant to the vaccine treatment of the rheumatic diseases.

In the preface to this second edition of his book the author states that great advances have been made in the treatment of the rheumatic diseases since the publication of the first edition and goes on to say " . . . It is significant that no change has been found necessary in the technique of vaccine therapy ". The confidence inherent in this statement manifests itself through the whole book and constitutes both its strength and its weakness.

Its forcefulness and wide appeal lie in the exact detail of its instructions regarding the handling of the different types of rheumatic disability. So long as the aetiology of this disability group remains obscure and its response to treatment unpredictable, so long will the problem remain a worry to the general practitioner dealing with individual treatment. This book contains much useful general information and practical advice apart from the detail regarding vaccine therapy, and its appeal is evidenced by the appearance of this second edition.

The author himself admits that some of the views expressed are individual and not acceptable to many of the recognized authorities in this field. Though modern thought has tended to swing away from the idea of infection as the primary factor in arthritis, the author claims that infection is the most important factor in all rheumatic conditions whether articular or non-articular. In his opinion osteo-arthritis is infective in origin and " the presence of a microbe is essential to the disease ". He also states that acute infective arthritis is distinct from rheumatoid arthritis from which it can be distinguished clinically and radiologically, saying that " in its later stages it becomes osteo-arthritis and is quite indistinguishable from it ".

His technique of vaccine therapy aims not at desensitization but, by small doses, at tissue sensitization or immunization, and at periodic stimulation. His technique of gold therapy is also by small doses (varying from 4 to 0·04 mg.) and he favours the colloidal preparations of the metal. He considers gold therapy to be akin to vaccine therapy in so far as its action is not chemotherapeutic but immunizing. Small dosage is also claimed to give the best results in local analgesic injection of tender spots. He advises that no more than 0·2 cc. be used of an 0·5 per cent. procaine solution.

Admirable and praiseworthy though such independence of thought and action may be, modern medicine demands that certain basic standards of assessment of improvement and measures of disability shall be satisfied and followed up over long periods before therapeutic claims can be justified. Clinical impressions and

assessment couched in vague terms (such as " much better ", " improved ", " results good ") are of no real significance in modern scientific investigation. The more thoughtful reader would like to see more evidence brought forward in substantiation of the therapeutic claims made. Such evidence would require follow-up reports and the use of standards of assessment of disability and progress adequate to the demands of modern research. The addition of such a chapter would add considerably to the value of this book. J. W. T. PATTERSON.

Arthritis and Allied Conditions. By the late B. I. Comroe, M.D. Rev. ed. by Joseph L. Hollander. 1949. London: Henry Kimpton. Pp. 1108. Illustrated. 80*s*.

Dr. Joseph Hollander has undertaken the considerable task of editing and revising the new edition of this well-known book. He has called to his aid a number of distinguished contributors. Though this book has always been a complete work of reference, it seemed to some, in former editions, lacking in critical appraisal, and all views were quoted without discrimination. This has been altered by the new editor and the value of the work greatly enhanced thereby. At the same time the extensive references have been kept up to date and the many photographs and drawings are as good as ever. One of the features of former editions were the clear tables on differential diagnosis throughout the book; these have been retained and extended, though some workers in this country would like to see one differentiating rheumatoid arthritis from ankylosing spondylitis.

Dr. Wallace Graham has written a first-class account of the painful shoulder with its problems of differential diagnosis and treatment, and also an excellent note on the organization of an arthritis clinic, which reflects the views of many in Great Britain.

Dr. Richard Freyberg has a well-balanced chapter on gold salt therapy, in which he weighs carefully the evidence for and against this form of treatment. He concludes that gold salts are of value if carefully controlled, but points out very clearly the complications which may occur.

Dr. Edward Boland has written an excellent chapter on the psychogenic factors in the rheumatic diseases, including psychogenic rheumatism, and this account, which is the result of his own and Hench's work in the army, will be carefully studied by many. He also deals with the subject of spondylitis, and gives a fine description of the natural history of the disease and its various clinical aspects.

Dr. Edward Rosenberg contributes on many subjects, including the pathological aspects and the visceral manifestation of rheumatoid arthritis, and gives excellent summaries of recent knowledge on these and the other matters with which he deals.

Many readers will turn with pleasure to the chapters by Dr. John Lansbury on the endocrine glands, allergy, and the collagen group of diseases. These are clearly written, and though short in the present edition will have to be expanded in the future. He sifts the arguments as to the role of allergy in the rheumatic diseases and concludes that we must " wait and see; since the pathogenesis of both

allergy and the rheumatic diseases is little understood, explaining one unknown in terms of another does not solve the problem ".

The two chapters on the collagen group of diseases are perhaps the outstanding new contribution to the book. The whole group is considered in a most lucid manner and each condition described with the utmost clarity. The editor himself has written or collaborated in many of the chapters. No rheumatologist can afford not to have this book, and young physicians who are turning with interest to this subject should study it carefully, as it is a major work of reference with many authoritative views included. W. S. C. COPEMAN.

ABSTRACTS

[This section of the ANNALS *is published in collaboration with the two abstracting Journa* Abstracts of World Medicine, *and* Abstracts of World Surgery, Obstetrics and Gynaecology, *published by the British Medical Associa on. The abstracts are divided into the following sections: acute rheumatism; chronic articular rheumatism (rheumatoid arthritis, osteo-arthritis, spondylitis, miscellaneous); sciatica; gout; non-articular rheumatism; general pathology; other general articles. At the end is a list of articles that have been noted but not abstracted. Not all sections may be represented in any one issue.]*

Acute Rheumatism

The Role of Sulphanilamide Prophylaxis in Rheumatic Fever. STOKES. L. (1949). *Med. J. Aust.*, **1**, 379.

In Melbourne 211 children were given prophylactic sulphanilamide or sulphadiazine, many for a period of 4 years. From the age of 7 to 12 years the dose of sulphanilamide was 0·5 g. twice a day, and that of sulphadiazine 0·5 g. once a day. There were no serious toxic complications.

In the sulphanilamide series, comprising 565 person-years, there were nineteen recurrences (3·4 per cent). In the control series, totalling 971 person-years, there were 115 recurrences, (11·8 per cent). The interval between the commencement of sulphonamide prophylaxis and the last major episode of rheumatic fever was less than 1 year in 62 per cent., 1 to 2 years in 26 per cent., and 2 years or more in 12 per cent. There was a significant reduction in the group A streptococcal carrier rate in the sulphonamide-treated group.

[It is not possible to assess the significance of these figures because insufficient details of the experiment are supplied. There is no mention, for instance, of how the controls were chosen.] *R. S. Illingworth.*

Spectacular Improvement Produced by Heparin in a Case of Acute Articular Rheumatism. (Amélioration spectaculaire d'un cas de rheumatisme articulaire aigu par l'héparine.) DONZELOT, E., KAUFMANN, H., CHARTRAIN, E., and NORY, J. (1949). *Bull. Soc. méd. Hôp. Paris*, **65**, 475.

A woman of 25 years, suffering from mitral disease, suddenly developed intense general joint pains with pyrexia (38° to 39° C.; 100·4° to 102·2° F.). After 2 months' illness, the disease was treated by giving heparin (150 mg. in 24 hours) intravenously for 3 days; the dose was doubled on the 4th and 5th days, and on the 5th day the pyrexia ended by crisis, the temperature subsequently being normal. With the end of the pyrexia the pains ceased and did not recur. On the 3rd to 8th days (that is, until 3 days after the end of the pyrexia) 0·75 g. of "3277 RP" ("phrenergan") was given in each 24 hours. For 6 days after the end of pyrexia, 5 million units of penicillin were given daily. Before this treatment the disease had proved resistant to both sodium salicylate (12 g. a day orally or 3 g. orally with 2 g. intravenously) and penicillin.

The paper was read only 9 days after the crisis of the disease and it is not therefore known how permanent this cure may be. [The erythrocyte sedimentation rate is not mentioned.] *Jeffrey Boss.*

Studies on Rheumatic Fever. Observations on Tonsillar Carriers of Haemolytic Streptococci; the Effect of Tonsillectomy and the Administration of Penicillin on Rheumatic and Nonrheumatic Fever Patients. NELSON, H. G., SEAL, J. R., BLACK, J. B., BAILEY, R. L., GRAETTINGER, J. S., COHN, P. D., and FRIOU, G. J. (1948). *J. infect. Dis.*, **83**, 138.

This study was carried out on two groups of patients undergoing tonsillectomy: (1) 75 men between 17 and 21 years of age transferred from naval centres in the north (where streptococcal infections were common) for convalescence from an attack of rheumatic fever; (2) 64 men from the surrounding country (Georgia) referred for tonsillectomy but without a history of rheumatic fever or tonsillitis within 1 month of admission. Cultures were taken from the throat and excised tonsil and from nasal secretion obtained by blowing the nose [for details see original paper], and Lancefield grouping and typing were carried out.

Of Group 1 cases 33·3 per cent. had group A haemolytic streptococci in the excised tonsil and 2·7 per cent. had these in the pre-tonsillectomy throat swab, compared with 15·6 per cent. and 3·1 per cent. respectively of patients in Group 2. These figures are not comparable with those of Rantz (1941) since three of the four patients in the present study had had penicillin treatment immediately before tonsillectomy and others in the rheumatic group had had penicillin previously.

In both groups of patients between 12 per cent. and 14 per cent. of the streptococci belonged to groups other than Lancefield A. Only five cultures could be typed. The incidence of tonsillar group A streptococci was the same in a series of 22 patients undergoing tonsillectomy while still in an active phase of rheumatic fever, and in 53 who were in the inactive phase as judged by absence of fever, arthritis, or arthralgia within 1 month of tonsillectomy. Both active and inactive subgroups recovered successfully from the operation; they received 40,000 units penicillin intramuscularly every 3 hours. The results of culture, erythrocyte sedimentation rate measurement, and Weltmann coagulation test showed a similar curve in both these subgroups of Group 1 and in Group 2. There was no adverse effect of this operation in any case.

It is concluded that culture from excised tonsils gives

more accurate data than do throat and nose swabs on the incidence of the streptococcal carrier state.

E. G. L. Bywaters.

Rheumatic Fever in the War and Post-war Periods. Ревматиэм в годы отечественной войны и в послевоенный период). BOGDANYAN, M.G. (1941). Клиническая Медицина. *Klin. Med., Mosk.*, **27**, 45.

This is a study of 109 cases of subacute bacterial endocarditis, 130 cases of recurrent rheumatic endocarditis, and 139 cases of heart lesions observed between 1940 and 1946; all cases came to necropsy during that period. The findings may be thus summarized:

(1) Rheumatic polyarthritis diminished in frequency from 1942 to 1945, when the incidence tended to rise.

(2) Rheumatic carditis followed this trend to a slighter degree.

(3) The incidence of "cardiac and arthritic rheumatism" fell in 1941 and continued to be low throughout the period. It is noted that during the revolution the incidence of arthritic rheumatism fell to a tenth of the figure in 1910, and the author associates this and the present fall with an insufficiency of diet, which in his opinion diminishes the incidence of articular rheumatism.

(4) In contrast with the above, there was an increase in the incidence of subacute bacterial endocarditis from 1943 onwards, so that the numbers of cases have exceeded those of recurrent rheumatic carditis in the last 3 years.

(5) In the group of bacterial infections, mitral and aortic lesions predominate, forming 33 per cent. of the whole. In the rheumatic group, the same lesions also predominate, forming 34·6 per cent. of all lesions. Mitral lesions come next, with 25·7 per cent. and 30 per cent. respectively in the two groups. Aortic lesions form 17·4 per cent. of those in the bacterial group, but only 10 per cent. of those in the rheumatic group.

(6) Infarcts in various organs occurred in most of the cases of bacterial infection (in from 86·6 per cent. to 100 per cent. in the separate years, and in 92·7 per cent. of the whole); they were also present in no less than 63 of the cases of rheumatic origin and in 48·9 per cent. of the cases without active rheumatism. Of all the 378 cases, 30·4 per cent. showed infarcts in the lungs, 21·4 per cent. in the spleen, 25·6 per cent. in the kidneys, 15·3 per cent. in the brain, 4·7 per cent. in the heart, and 36·2 per cent. in various organs, including the peripheral vessels.

L. Firman-Edwards.

Relation of the Haemolytic Streptococcus to Rheumatic Fever. IV. Effect of Streptococcic Spreading Factor in Rheumatic Patients and Others. HARRIS, T. N., and FRIEDMAN, S. (1949). *Amer. J. Dis. Childh.*, **77**, 561.

Hyaluronic acid is capable of enzymic digestion by hyaluronidase, and a similar enzyme or spreading factor is produced by the haemolytic streptococcus. It was stated by Guerra (*Science*, 1946, **103**, 686; *J. Pharmacol.*, 1946, **87**, 193) that hyaluronidase caused a far greater spread of dyes in the skin of rheumatic patients than in that of normal subjects, but this has not been confirmed by the present authors.

The material used in this study was a dessicated preparation of spreading factor and proteins from the H 44 strain of group A haemolytic streptococcus, with a solution of human haemoglobin as indicator. The method of preparation and assay of the material is described in detail. Initial tests were carried out on rabbits.

In the clinical investigation 25 mg. of hyaluronidase-containing streptococcal proteins in 0·05 ml. of haemoglobin solution was injected intradermally into 33 children with rheumatic disease and 28 control children. Control injections of haemoglobin solution alone, and either a solution containing spreading factor alone or a solution containing haemoglobin and heated spreading factor, were also made in each case. The area of spread at the end of 1 hour was measured, and also the inflammatory reaction after 24 hours. No appreciable difference in spread was found between the normal inactive rheumatic, and active rheumatic groups.

The authors consider that the amount of the injection was enough to demonstrate an increased sensitivity to hyaluronidase, since some spread was produced in the controls. They suggest that Guerra's results differed because the larger injections which he used caused massive inflammatory reactions, probably due to the accompanying proteins and not to the hyaluronidase, and that this gave a false spreading effect.

Kathleen M. Lawther.

Incidence of Rheumatic Disease and Subacute Bacterial Endocarditis during the War and the Post-war Period. (О частоте заболеваемостн ревматиэмом и подострым септическим эндокардитом в период великой отечественнои войны). ETINGER, Y. G., and SCHMERLING, M. G. (1949). *Terap. Arkh.*, **21**, No. 2, 15.

The incidence of rheumatic disease considerably diminished in Russia during the late war, whereas during the post-war period there has been a tendency to increase again. The authors observed a sharp fall in the incidence of the polyarthritic form of rheumatism amongst adults. In 1940, 3·4 per cent. of all patients in their clinic in Moscow were suffering from the polyarthritic type of rheumatism. During the war years on the average 0·25 per cent. of all patients had rheumatic polyarthritis, an incidence fourteen times less than that in 1940. The lowest figures were obtained in 1944, with an incidence of only 0·1 per cent. During the war there was also a marked decrease in the cardiac form of rheumatism (non-arthritis type) amongst adults, but the decrease was not so substantial as that of polyarthritis.

Statistics also show that there was a marked decrease in the incidence of cardiac forms of rheumatism among children. The mortality from cardiac affections in children was ten times lower than in the pre-war period. The incidence of chorea during the war was only one-tenth of that in the pre-war period. The incidence of subacute bacterial endocarditis during the war did not show any substantial change, but it increased almost three-fold during the post-war period.

The reason for these decreases in incidence are not clear. The haemolytic streptococcus may have had a low virulence during the war, but other causes such as change of diet no doubt played their part.

H. W. Swann.

Quantitative Studies on the Total Plasmin and the Trypsin Inhibitor of Human Blood Serum. II. Variations in the Blood Concentration of Total Plasmin and of Trypsin Inhibitor in Streptococcal Diseases with Special Reference to Rheumatic Fever. TODD, E. W. (1949). *J. exp. Med.*, **89**, 309.

Repeated estimations were made of plasmin and trypsin inhibitor in the serum of young men with scarlet

fever. In uncomplicated cases plasmin curves were considerably higher than inhibitor curves; in cases with purulent complications the curves were closer together; in cases in which rheumatism developed the curves were close together and the inhibitor curve rose above the plasmin curve at the time of rheumatic activity. It is suggested that plasmin and inhibitor are normally linked by a compensatory mechanism, which is disturbed in cases in which rheumatism develops. *J. R. Marrack.*

Involvement of the Lung in Rheumatic Fever. (Sobre la participación del pulmón en la fievre reumática.) ESTRADA GONZÁLEZ, R. (1949). *Arch. Hosp. univ. Habana*, **1**, 75.

An analysis is made of seventeen fatal cases of rheumatic fever, in six of which interstitial pneumonia was present. The difficulty of diagnosis in the absence of cardiac and articular symptoms is stressed, and it is suggested that differentiation from primary atypical pneumonia can be made only by tests for antistreptolysin and cold agglutinins. *George Hickie.*

The After-history of Juvenile Rheumatism Patients. WOODROFFE ANDERSON, C. (1948). *Med. Offr.*, **80**, 261.

An inquiry was made into the general health, recreation, and national service record of people who not less than 15 years previously had been treated in a hospital for children suffering from juvenile rheumatism. The inquiry was carried out in the homes by nurses, and is therefore not clinical, but rather correlates subsequent health with previous clinical findings in hospital.

The commonest forms of rheumatism treated were rheumatic pains and chorea. In one-third of cases admitted to hospital the heart was normal, in one-third very slightly abnormal, and in one-third definitely so. Three months' stay in hospital raised the number of normal hearts to 87 from fifty. However, the condition in a few cases deteriorated and there was evidence of severe heart disease on discharge from hospital. Of 167 patients reported upon, 21 had died. Of the remainder 108 were in good, 32 in fair, and six in bad health.

Group A—63 married women. Of 63 discharged from hospital with a normal heart, 44 were in good, sixteen in fair, and three in bad health. Nine had had no pregnancies since marriage. In the remaining 54, 102 pregnancies had resulted and health was good in 45, fair in six, and bad in three. There were 81 normal births, seven miscarriages, five stillbirths; nine were not yet confined. All patients were engaged in strenuous or moderate full-time work before and/or after marriage. No patient reported incapacity for work; 50 per cent. took an active part in sport.

Group B—29 unmarried women. General health was reported good in eighteen cases, fair in ten, and bad in one; 28 were occupied full-time and 50 per cent. enjoyed active recreation.

Male patients in groups C and D were with one exception all engaged in full-time strenuous or moderate work; all but thirteen took part in sport. Group C—39 men fit for war service. Of these 31 served abroad in all theatres of war. In all 39 general health was reported good; they were fully employed in strenuous work and the majority were active sportsmen. Group D—fifteen men exempt from war service. Although exempt from war service, only two reported bad health, and with one exception, an arthritic cripple, all were capable of heavy or moderate full-time work and over 60 per cent. were active sportsmen. Only five claimed exemption from war service on grounds of rheumatism or heart disease.

Group E—21 deceased (nine males and twelve females). Eleven deaths were reported due to heart disease. Only one of these patients had had a normal heart when first examined. The result of delay in the early recognition and treatment of juvenile rheumatism is indicated by the progressive deterioration in the condition of these patients, nine of whom were already suffering from severe heart disease by the time they left school. All had died by the age of 24½ years. *J. Greenwood Wilson.*

The Differential Diagnosis of Rheumatic Fever and Infections of the Central Nervous System. BRAINERD, H. D., and SOKOLOW, M. (1949). *J. Pediat.*, **34**, 204.

The authors draw attention to the occurrence, in some cases of rheumatic fever, of (1) neck stiffness, a positive Kernig's sign, and muscle spasm, leading to the erroneous diagnosis of an infection of the central nervous system: and (2) refusal to move a limb, on account of painful arthritis, leading to a mistaken diagnosis of poliomyelitis. They mention the occasional confusion of rheumatic fever with meningococcal infections, and emphasize the importance of a search for petechial haemorrhages and for the characteristic rash in meningococcal septicaemia, and of making a blood culture in cases of doubt. *R. S. Illingworth.*

Bacteriologic and Immunologic Studies on Patients with Haemolytic Streptococci Infections as Related to Rheumatic Fever. ROTHBARD, S., WATSON, R. F., SWIFT, H. F., and WILSON, A. T. (1949). *Arch. intern. Med.*, **82**, 229.

The authors studied 153 patients in whom 169 acute haemolytic streptococcal infections of the upper respiratory tract occurred; rheumatic fever developed in 38 (in 21 cases as a primary infection and in seventeen in previously rheumatic subjects). Variations in antistreptolysin O, antifibrinolysin, and type-specific bacteriostatic antibody titres, as well as in the level of precipitins the type-specific M substance, the group-specific C substance, the C-reactive protein, and the nucleoprotein of haemolytic streptococci, were studied at frequent intervals in 71 patients. Significant rises in antistreptolysin O titre occurred in 77 per cent., in antifibrinolysin titre in 73 per cent., in bacteriostatic antibody titre in 76 per cent., in anti-M precipitin level in 64 per cent., and in C-reactive protein content in 71 per cent.; antistreptolysin O, antifibrinolysin, and type-specific antibody titres rose more frequently in patients with rheumatic fever than in those who had purulent complications or who made uneventful recoveries. Nevertheless, there is at present no single pattern of antibody response which can be used to diagnose the existence of rheumatic fever. *R. Hare.*

Left Atrial Calcification in Rheumatic Heart Disease. EPSTEIN, B. S. (1949). *Amer. J. Roentgenol.*, **61**, 202.

This paper records three cases in which calcification in the wall of the left auricle was diagnosed radiologically

in patients with long-standing rheumatic heart disease with mitral stenosis and insufficiency.

The first was a 45-year-old woman. On radiological examination the whole atrial wall could be seen as a thin, roughly spherical shell. In the postero-anterior view the ring shadow lay entirely within the enlarged cardiac contour, the right wall of the atrium approaching the right border very closely, the left wall being separated by a rather greater interval from the left cardiac border. The auricular appendix was not calcified. The right oblique view showed displacement of the barium-filled oesophagus, but the author notes particularly that the calcified shadow met the oesophagus only at the point of maximum protrusion. The thickness of the ring shadow was 2 mm. at its greatest. Some calcification was present also in the mitral valves, which were displaced downwards. The second patient, a woman aged 35, had greater atrial dilatation; the left border of the left atrium was seen as a crescentic line of calcification beyond the left ventricular border, while the left atrium also formed the right border of the heart shadow. Calcification, both in this patient and in the third, a woman aged 39, was less complete than in the first case and was mainly in the left and posterior walls of the atrium. The author suggests that the lime salts had been deposited in plaques of damaged atrial endocardium, such as were originally described by MacCallum (*Bull. Johns Hopk. Hosp.*, 1924, **35**, 329, and *J. Amer. med. Ass.*, 1925, **84**, 1545).

A. M. Rackow.

Rheumatic Infection in Childhood: Fifteen to Twenty Year Follow-up. Caution Against Early Ambulant Therapy. ASH, R. (1948). *Amer. J. Dis. Childh.*, **76**, 46.

A series of 331 rheumatic children was followed up for 15 years from the onset of infection, and 150 children for 20 years. After 15 years 55·9 per cent. were leading a normal existence, 4·5 per cent. were limited in activity, and 37·4 per cent. had died of rheumatic infection or bacterial endocarditis. Of the 150 children who were followed up for 20 years, 52·6 per cent. had died, 41·3 per cent. were leading a normal existence, and 3·3 per cent. were suffering from congestive heart failure. [According to the table 55·3 per cent. have died.] The incidence of carditis and of deaths within the first 10 years was greater among those taken ill during the period 1923 to 1927 than during the years 1928 to 1932, and least of all among those taken ill during the years 1933 to 1937. The author argues that the more prolonged period of rest in bed employed in recent years is a more important factor in this improvement than spontaneous changes in the character of the disease. [Spontaneous changes in the character of diseases due to infections are so important that it is never wise to make deductions about the effect of treatment by comparing the mortality rate in one period with that in another.]

R. S. Illingworth.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

The Subcutaneous Nodules of Chronic Rheumatoid Arthritis: Their Clinical and Pathological Features. HORWITZ, M. (1949). *Clin. Proc.*, **8**, 73.

The subcutaneous nodules in rheumatoid arthritis have not been so extensively studied and their nature investigated as have the better-known subcutaneous nodules found in acute rheumatic fever. In the investigation reported, seventy cases of chronic rheumatoid arthritis were studied, 47 in female and 23 in male patients whose ages ranged between the extremes of 9 years and 77 years. The duration of the disease at the time of examination also varied from 7 months to 45 years, the average duration being approximately 7 years. All the cases were carefully considered from the clinical aspect, and the author states that they could all be regarded as examples of what he refers to as "true 'idiopathic' polyarticular rheumatoid arthritis"; these patients had been under intermittent observation for periods of 6 to 18 months and the clinical diagnosis was subject to radiological confirmation.

One or more nodules were found in twenty of the seventy cases, a total of 99 nodules, situated most frequently over the olecranon process or ulnar border of the forearm, being noted. Nodules were also found not infrequently on the fingers and in other less common sites, and often reached a considerable size. They were sometimes lobulated—particularly when they occurred over the olecranon bursa. In the case histories, trauma seemed to play a part in nodule production, but their incidence was greatest in those advanced cases in which considerable crippling had occurred. Their relation, if any, to the prognosis of the disease is not yet determined. Biopsy of sixteen nodules showed the characteristic histological appearance described by previous authors, and amyloid changes could not be detected. The author comments on the striking resemblance clinically between the nodules and those of xanthoma tuberosum and planum. He does not consider the necrobiotic foci seen as being specific for rheumatoid arthritis.

W. S. C. Copeman.

Rheumatoid Arthritis in the Young. SCHLESINGER, B. (1949). *Brit. med. J.*, **2**, 197.

Clinical observations were made in twenty cases of acute rheumatoid arthritis in children, all of whom suffered from considerable fever and the usual general acute manifestations first described by Still. Nearly all were studied early in the disease or from the onset, and their subsequent progress was followed for many years. Detailed observations on the early clinical features—the initial migratory arthritis, adenitis, splenomegaly, and fever—are recorded, and the widespread nature of the lesions is emphasized. Significant effects on the blood picture have been observed, and also rare instances in which the clinical picture changes from Still's disease to leukaemia. In the majority of cases the condition proceeds to progressive arthritis, but some patients recover completely.

The relationship of this disease to certain rare syndromes of an allergic nature is considered. The author finds points of resemblance in intermittent hydrarthrosis, palindromic rheumatism, lupus erythematosus, and polyarteritis nodosa.

K. Stone.

Rheumatoid Arthritis and the Function of the Joints. [In English.] DAHLBERG, G., and SUNDELIN, F. (1949). *Acta med. scand.*, **135**, 40.

An attempt was made to discover why rheumatoid arthritis affects some joints more frequently and more severely than others. A statistical survey was carried

out on 1,002 patients, 680 women and 322 men, who were also grouped according to whether they did heavy or light work. The various joints first affected were noted and comparisons made between right and left sides and upper and lower limbs; finally, an attempt was made to correlate these findings with the type of work performed and the patient's sex.

No results of statistical significance were obtained and in these patients there was no evidence that the work done by any particular joint bore any relation to the subsequent development of rheumatoid arthritis.

Winston M. L. Turner.

Intensive Chrysotherapy (with Lauron) in Rheumatoid Arthritis. FRIEDMAN, H. H., and STEINBROCKER, O. (1949). *New Engl. J. Med.*, **240**, 362.

The effect of large doses of aurothioglycanilide ("lauron") over a short period is assessed in eighteen cases of rheumatoid arthritis. In one case complete remission, and in two cases slight improvement, occurred as an immediate result of treatment, and in two cases remission of signs and symptoms occurred 3 and 6 months respectively after treatment had ceased. The remaining thirteen patients received no benefit. The authors conclude that large doses of lauron over a short period do not appear to have any spectacular effect on the disease. *Kathleen M. Lawther.*

Pulmonary Lesions in Rheumatoid Arthritis. LEYS, D. G., and SWIFT, P. N. (1949). *Brit. med. J.*, **1**, 434.

In a case of juvenile rheumatoid arthritis a transient diffuse pulmonary lesion formed an intimate part of the disease. The arthritis was severe and progressive, and the child was treated with two courses of "myocrysin" and repeated small blood transfusions. The pulmonary episode occurred about 8 months after the onset of the condition and was accompanied by intermittent pyrexia lasting approximately 2 weeks. There was no leucocytosis or eosinophilia. The authors consider that the lung condition and also the other manifestations of rheumatoid arthritis are only part of an allergic state in which familial and environmental, factors play a part. *Richard D. Tonkin.*

Therapeutic Criteria in Rheumatoid Arthritis. STEINBROCKER, O., TRAEGER, C. H., and BATTERMAN, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.

The paper summarizes the recommendation of the Committee for Therapeutic Criteria of the New York Rheumatism Association proposing the adoption of uniform systems of classification of the stages of progression, degree of functional impairment, and response to treatment.

Gold Stomatitis. Acute Ulcerative Buccal Lichen Planus Treated by BAL. (Stomatite aurique. Lichen plan aigu ulcéreux buccal biotropique traité par le B.A.L.) MORDANT, —. (1949). *Arch. belges Derm. Syph.*, **5**, 63.

The author reports a rapid cure when BAL was used in the treatment of a case of lichen planus-like stomatitis occurring during the treatment of polyarthritis with gold. *James Marshall.*

(Osteo-arthritis)

Degenerative Osteoarthritis of the Hip Joint. Survey of Degenerative Arthritis Secondary to Aseptic Necrosis of the Femoral Head. HORWITZ, T. (1949). *Arch. Surg. Chicago*, **58**, 251.

The author reviews the subject of osteo-arthritis of the hip with thoroughness in the light of 81 personal cases. The presenting symptom is pain, and the well-recognized diagnostic signs appear later. He subdivides cases into those of uncomplicated osteo-arthritis and those precipitated by aseptic necrosis of the femoral head.

Various forms of arthroplasty were carried out in 33 cases, but the results, on the whole, were poor. The results were more encouraging when arthrodesis was attempted; out of 22 cases solid fusion, almost synonymous with good function, was obtained in fifteen. It is the general opinion that a previous pathological condition is recognizable in about half the cases. The underlying condition may be a congenital dysplasia, a slipped epiphysis, or Perthes's disease. Sometimes the osteo-arthritis is merely an expression of senescence. There is no essential difference in pathology between these two types. Aseptic necrosis of the femoral head usually follows major displacements, but occasionally no cause can be found.

Because of the pathological changes in aseptic necrosis it is not difficult to understand why treatment is not effective. Treatment is directed to dealing with the inevitable arthritis that follows. Anthroplasty, in its various forms, is apt to be disappointing because the condition may be progressive after operation. Arthrodesis gives more reliable results but because of the state of the femoral head some form of extra-articular procedure is called for.

Where arthritis is bilateral, the problem is more complex and in these cases some form of excision combined with an osteotomy is usually called for. [As a study of osteo-arthritis of the hip this article is to be recommended.] *Ronald Furlong.*

Observations on Heberden's Nodes. (Contributo alla conoscenza dei noduli digitali di Heberden.) ROBECCHI, A., and PINO-SACCA, F. (1949). *Rev. Rhum.*, **16**, 132.

The authors studied nine fingers on which Heberden's nodes were present. The fingers were removed from the bodies at necropsy and the authors knew nothing of the cause of death of these patients. The histological changes were identical with those of osteo-arthritis.

(Spondylitis)

Spondylitis, Pathological Ossification, and Calcification Associated with Spinal-cord Injury. ABRAMSON, D., and KAMBERG, S. (1949). *J. Bone Jt Surg.*, **31A**, 275.

Certain skeletal changes are frequently seen in patients suffering from complete transverse lesions of the spinal cord above the level of the first lumbar vertebra. These include sclerosis around the sacro-iliac joints, often amounting to fusion, new bone formation around the hip-joints and at the ischial tuberosities, soft-tissue calcification in the buttocks, degeneration and fusion of the lumbar apophysial joints, and variable porosis and sclerosis of the lumbar vertebral bodies. The causes are

the demineralization of immobilization in recumbency and the neurotrophic factor, and it is noteworthy that significant changes are not seen in partial lesions of the cord at any level, nor in complete lesions of the cauda equina. *David Le Vay.*

d-Tubocurarine in Oil-Wax Suspension in Rheumatoid Spondylitis. Its Use as an Adjuvant. NORCROSS, B. M., ROBINS, H. M., and LOCKIE, L. M. (1949). *J. Amer. med. Ass.*, **140**, 397.

The authors suggest that, while reflex muscle spasm occurs in order to protect the vertebral structures, it is in itself painful and leads to the establishment of a vicious circle whereby vertebral pain produces muscle spasm and muscle spasm perpetuates the pain. The authors sought means to relieve the muscle spasm, and found that, while a watery solution of curare gave relief, the relaxation obtained was transient and was accompanied by " the unpleasant side-effects of curarization ". They therefore decided to try injections of a suspension of *d*-tubocurarine in oil-wax as advocated by Schlesinger in certain " acute low back syndromes ".

Tubocurarine apparently acts by blocking the myoneural junction by raising its threshold for acetylcholine above the normal level. The aim of curarization is to block abnormal reflex stimuli but permit the passage of normal voluntary stimuli. The authors used a preparation containing 3 per cent. *d*-tubocurarine in a mixture of 4·8 per cent. wax in peanut oil. Dosage is an individual problem, and the effect aimed at is to obtain muscular relaxation by a low initial dose and higher subsequent doses at 24- to 48-hour intervals. After this, further injections are given when muscular spasm recurs. There are potential dangers associated with the use of the drug, and rules are given to avoid them. Should toxicity occur, injections of neostigmine are advocated, but the authors consider that if precautions are taken the dangers of toxic manifestations are minimal.

They describe the treatment of six patients with severe muscle spasm manifested by bursts of abnormal activity in electromyographic recordings. It is claimed that injections of *d*-tubocurarine led to relief of pain, increase of mobility, and correction of flexion deformity. " Practically no toxicity " was met with in this series. *W. Tegner.*

Statistical Studies of the Early Symptoms of Ankylosing Spondylitis. (Études statistiques sur les symptomes de début de la spondylarthrite ankylosante.) FORESTIER, J., JACQUELINE, F., and ROTES, J. (1949). *Rev. Rhum.*, **16**, 218.

This paper contains a valuable analysis of the initial symptoms observed in 200 cases of spondylitis in 164 males and 36 females. Symptoms began in a few of these cases between 11 and 15, in a large number between 16 and 20, and in very few after 40 years. The initial symptom (those listed below were among those found by the authors) may remain the only manifestation for months or years.

Sciatic pain was observed more frequently at the beginning than during the established disease, and was a peculiarly common symptom in the younger patients; repeated attacks might occur for many years, usually unilaterally, but sometimes occurring alternately on the right and left sides. In most cases arthritis of rheumatoid type was mono-articular or oligo-articular, shoulders, hips, and knees being most frequently affected. It is interesting that 78 per cent. of the females and 56 per cent. of the males had an affection of the peripheral joints either at the onset or during the established disease. The erythrocyte sedimentation rate during the stage of early symptoms was normal in about 25 per cent. of cases in which it was determined. *Kenneth Stone.*

Initial symptom	No. of cases	Occurring as an isolated symptom
Lumbar pain	80	21
Sacro-iliac pain	25	6
Dorsal pain	26	2
Cervical pain	17	4
Intercostal pain	22	2
Sciatic pain	50	21
Transient joint pains	46	24
Arthritis of rheumatoid type ..	53	27

(Miscellaneous)

The Vertebral Tomogram. (Le tomogramme vertébral.) DE SÈZE, S., and DJIAN, A. (1949). *Rev. Rhum.*, **16**, 311.

This paper is based on an analysis of 1,000 tomograms of various types of normal vertebrae. The technique is briefly outlined and the most characteristic images are described. The method proved most useful for the examination of those parts of the spine which are difficult to demonstrate on routine radiographs, such as the cervico-dorsal region. The various elements of a vertebra can be easily studied when isolated by tomography. *A. Orley.*

The Value of Tomography in the Investigation of Vertebral Disease. Comparison of Standard Radiographs with Tomographs of the Vertebrae. (De l'intérêt de la tomographie dans l'analyse des affections vertébrales. Confrontation de radiographies vertébrales classiques et en coupes.) WEIL, M. P., and DJIAN, A. (1949). *Rev. Rhum.*, **16**, 323.

This is a comparative study of straight and tomographic pictures in five cases of vertebral arthritis. In each of the cases tomography helped to elucidate a number of topographic and anatomo-pathological data and generally facilitated interpretation of the radiographic findings. *A. Orley.*

Sciatica

The Mechanism of the Intervertebral Disc Protrusion. LEWEY, F. H. (1949). *Surg. Gynec. Obstet.*, **88**, 592.

In 169 cases of protrusion of the intervertebral disk treated by excision at the University Hospital of Pennsylvania, the histology of the disk was studied and compared with that of twenty controls. Of the 169 patients, forty have been followed-up for a period of years. The microscopical appearances suggested that lesions

of the disk may be grouped into three classes, occurring with approximately equal frequency: " bulging " disks, herniating disks, and " slipped " disks. The " bulging " disk presents as a bulge without any visible lesion of the annulus fibrosus or of the cartilage, and appears to correspond to the so-called " hidden " disk. Material removal from disks of this type consists of normal disk tissue. The results of operation upon such cases are poor, only about one patient in three being cured. The true herniating disk shows a rent in the annulus with disk material protruding from it and a spinal nerve-root hooked over this. Microscopical examination shows various degrees of necrosis and of liquefaction of the disk material. Removal of the protrusion is very successful, four patients out of five being completely cured. In the third group an eccentric posterior portion of the disk will be found to have slipped backwards from its attachments to the bony surfaces. In this type of protrusion the disk has a completely different histological appearance. The removed material consists of part of the epiphyseal plate and may, therefore, contain bone, the disk material attached to it being usually degenerate. Removal of the disk in this type of case is moderately successful and cures about one-half of the patients.

The writer concludes that the bulging disk is not in itself a cause of sciatica and supports the view that it should only be attacked surgically if a posterior nerve-root is clearly compressed by it. In cases of sciatica associated with the bulging disk, but without evidence of root compression by the disk, the cause must lie elsewhere, although it is recommended that the root should in such cases be thoroughly decompressed. Such bulging disks have been found at necropsy in 28 per cent. of 75 patients who had never complained of sciatica (Horwitz, *Surgery*, 1939, **6**, 410) and it is noted that, in the main, patients who are operated upon and found to have bulging disks have been complaining more of backache than of sciatica. In cases of true herniating disk, removal of the protrusion and freeing of the root should be enough to cure the patient. Anatomical considerations are discussed which suggest that curettage of disk material which is not protruding is irrational and unnecessary and, together with the histological findings, support the view that the protruding material includes degenerating tissue from the disk itself and not solely from the nucleus pulposus. The slipped disk is a puzzle and is best explained as a fracture of the disk and of the epiphyseal plate as a result of a torsion injury. The degeneration seen in the removed material is regarded as secondary to the trauma. No indication of primary disease of the disk was found in any of the material examined. *D. Ll. Griffiths.*

Surgical Treatment of Prolapsed Intervertebral Disks. (Zur chirurgischen Behandlung des Nucleus-pulposus-Prolapses.) HOFMANN, A. (1949). *Z. bl. Chir.*, **64**, 35.

The chief assistant of the Hafenkrankenhaus, Hamburg, gives a detailed account of his operative technique developed in some 170 cases of prolapsed disk. He differentiates between prolapse of the nucleus pulposus alone and prolapse of both the nucleus and part of the annulus fibrosus, and considers this sub-division as important but admits that mixed forms occur. He postulates three stages of either variety, the temporary or reversible form which may yield to conservative measures, and the complete form, which may be either " strangulated " or " detached " in both varieties. In strangulation no slipping back can occur because the " neck " of the prolapse is permanently trapped. Detachment means that the prolapsed portion is severed from the remainder, lies loose outside the annulus, and in certain instances " migrates " to atypical positions. Cases of ossification, both of the nucleus and of the annulus, are occasionally found.

There are considerable variations in the width of the space between adjoining vertebral arches; this matters particularly to those attempting operation through an interlaminar window. The variations within and outside the normal in the thickness of the ligamentum flavum are considerable; the author measures these in every case. The existence of firm narrow strands of fibrous tissue suspending the dura from nearby areas of bone is mentioned. (If these minute bands are not recognized and divided, the dura may be torn.)

The author operates with the patient in the prone position and uses local analgesia for the interlaminar approach. The increase in root pain felt by the patient when pressure is exerted on the ligamentum flavum or the prolapsed disk—if the latter is visible at this stage—is considered a valuable aid in location. " Evipan " is now added for the further stages of the operation which at first is always interlaminar only, but is often extended into a very restricted form of unilateral or bilateral laminectomy. The author's principle is to expose as much as necessary, but as little as possible. In removal of the prolapsed disk the author insists on gentleness and on the need not to be content with the removal of one loose part. In cases of " fragmentation " several parts may have to be searched for by curettage of the intervertebral space. In a few cases of extensive adhesion and fibrosis of nerve roots a root was divided without harm. In many cases the author injects the root with procaine. If the ligamentum flavum is not excised it should be stitched in place, since otherwise it may roll inwards and produce new pressure symptoms. After operation he recommends rest for one day in the prone position and for a fortnight to three weeks in alternating lateral positions.

Two patients died from staphylococcal infection. (The author does not use non-touch technique, and penicillin was not available.)

[This paper gives the experience of a surgeon cut off from most of the modern literature on the subject and from some of the aids enjoyed outside Germany. The author is a general surgeon and co-operates with a neurologist. He has collaborated already in publishing a paper (Otto, *Mschr. Unfallheilk.*, 1938, No. 10) which is not widely known. Some of his illustrations are very good indeed.] *L. Michaelis.*

Results of Operations for Lumbar Protruded Intervertebral Disc. RAAF, J., and BERGLUND, G. (1949). *J. Neurosurg.*, **6**, 160.

Between 1938 and 1947 one of the authors operated on 224 cases of lumbar disk protrusion. In cases in which diagnosis is in doubt the authors favour

myelography with " pantopaque ". There were no post-operative deaths, but two patients have died of unrelated causes. A second operation was performed in five cases. Analysing 160 cases followed up, the authors consider that in 98 (61 per cent.) the result was excellent, in 46 (28 per cent.) good, and in sixteen (10 per cent.) poor. An excellent or good result is more likely to follow when a protruded intervertebral disk is found and removed than when the exploration is negative or reveals some other pathological condition, such as adhesions about a root. Spinal fusion was carried out on a number of patients. The indications for this operation were severe back pain, spondylolisthesis, a lateral defect in the neural arch, an inequality of the angle of articulation of the facets on the two sides, or other evidence of instability. Pre-operative clinical diagnosis was correct in 81 per cent. *Lambert Rogers.*

Dilatation of the Veins of the Sciatic Nerve. (Расширение вен седалишного нерва). MARGORIN, E. M. (1949.) *Arkh. Patol.*, **11**, No. 2, 37.

Sciatic nerves were examined in a series of forty necropsies. Dilatation of endoneural and epineural veins was seen in twelve preparations. This dilatation did not always coexist with subcutaneous varicose veins. In two of the advanced cases, in which the venous extasia amounted to gross varicosity, degenerative changes were also seen in the nerve fibres. *L. Crome.*

The Advantages of Non-mutilating Techniques in Surgical Treatment of Sciatica. (Remarques sur les avantages des techniques non mutilantes dans le traitement chirurgical de la sciatique.) DE SÈZE, S., GUILLAUME, J., MAZARS, G., and JURMAND, S. H. (1949). *Sem. Hôp. Paris*, **25**, 927.

Of a series of 375 laminectomies for sciatica twelve gave mediocre results and six failed to relieve the pain of patients with prolapsed intervertebral disks. These eighteen bad results (5 per cent. of the total cases) occurred almost solely in very chronic cases with arthritis of the spine. The authors consider that failure to remove an osteo-arthritic rim around the disk hernia may be an important cause of the poor result.

In 230 patients the result of the operation, though good, was imperfect. These patients were all well satisfied with the relief they obtained, but they had residual symptoms—either paraesthesiae or backache. The paraesthesiae did not resemble those before operation and were usually transient. The authors attribute these to radiculitis. Persistent postoperative backache was a more important symptom. This pain was not of the same quality as the original lumbago, but was described more as a sense of fatigue. Some of these aches may be due to operative injury to intervertebral joints, but surgical injury to the spinal muscle mass is considered an important cause of persistent backache.

In a second series of eighty operations performed by an inter-myo-laminar approach (*see abstract below*), four were followed by transient paraesthesiae in the sciatic area. Only four other patients developed the sort of backache which was common after the older operation. The remaining 72 patients declared themselves free from symptoms. *D. Ll. Griffiths.*

Treatment of Sciatica due to Disk Prolapse by an Inter-myo-laminar Approach. Operative Technique. (Traitement de la sciatique discale par voie inter-myo-laminaire: technique opératoire.) GUILLAUME, J., MAZARS, G., and MASSEBOEUF, A. (1949). *Sem. Hôp. Paris*, **25**, 931.

This paper describes in detail the inter-myo-laminar operation recommended in the previous paper (*see above abstract*). The patient is placed in the lateral position, with the painful side uppermost, and the operation performed under local analgesia reinforced with light thiopentone anaesthesia. The landmark indicating the lumbo-sacral disk space is a line joining the two posterior superior iliac spines. The skin incision centres on this line. The lumbar aponeurosis is incised 5 mm. from the spinous processes and the erector muscle mass is split by blunt dissection and digital separation between the muscle bundles to the depth of the laminae. This leaves a thin sheet of intact muscle medially on the sides of the spinous processes and interspinous ligaments. The ligamentum flavum is exposed. It is detached from the two laminae concerned together with a thin fringe of bone which is cut off the edge of the laminae with a small gouge. This usually exposes the protrusion, most commonly found under the fifth lumbar lamina. A formal laminectomy is not performed; the approach really constitutes a fenestration. [The paper is very clearly illustrated.] *D. Ll. Griffiths.*

Gout

Production of Acute Gouty Arthritis by Adrenocorticotropin. HELLMAN, L. (1949). *Science*, **109**, 280.

Because the excitants of an acute crisis in the gouty subject—trauma, infection, surgical operation, and radiotherapy—have been shown to produce increased adrenal cortical activity (" the alarm reaction "), the author gave four gouty patients pituitary adrenocorticotrophin. In three out of five trials an acute attack of gout followed in 3 to 4 days with electrolyte and water charges identical with those described by Talbot and Coombs (*J. Amer. med. Ass.*, 1938, **110**, 1977) as " the gout cycle ". But during an acute attack adrenocorticotrophin caused a prompt disappearance of the acute arthritis.

The author suggests that stimulation of adrenal cortical function is the common pathway by which acute exacerbations of gout result from non-specific stress, and that adrenocorticotrophin may be useful as a provocative and therapeutic agent in gout. *Henry Cohen.*

Non-articular Rheumatism

Scapulo-humeral Periarthritis of Rheumatic Origin. (La périarthrite scapulo-humérale rhumatismale.) OTT, V. R., and WEIDERKEHR, J. (1949). *Rev. Rhum.*, **16**, 187.

The pathology of periarthritis of the scapulo-humeral joint is discussed, and the hypothesis is suggested that in those cases in which the affection is not due to trauma the essential condition is ischaemia of periarticular structures. The authors found that the most effective measure during the acute phase of the disorder is the local application of cold. *Kenneth Stone.*

General Pathology

The Synovial Membrane of the Knee in Pathological Conditions. SOEUR, R. (1949). *J. Bone Jt Surg.*, 31A, 317.

There are four histological types of synovial membrane: (1) an adipose type covering the articular fat pads; (2) a fibro-areolar type overlying areas subjected to moderate pressure and pull; (3) a fibrous type covering ligaments and tendons; and (4) a muscular type covering the suprapatellar pouch. The present study is concerned with the adipose type.

According to the author, it is now established that the synovial membrane is derived from the mesenchyma and is neither epithelium nor endothelium, and that its chief function is similar to that of the reticulo-endothelial tissues, its mechanical functions being of secondary importance. The adipose synovial membrane consists of a single layer of cells resting on an external adipose layer. The cells of the intima are flattened out, well spaced, and separated by an interstitial, homogeneous non-fibrillar substance with the staining reactions of collagen. The external layer is typical adipose tissue crossed by fine collagenous fibres. A capillary network joins the two layers, and larger vessels are seen in the external layer.

The adipose synovial membrane was studied clinically and experimentally in three conditions: (1) rupture of the menisci; (2) traumatic haemarthrosis; and (3) chronic hypertrophic villous arthritis. The author summarizes the changes in these three conditions as follows: (1) Meniscal tear: (*a*) synovial activity is marked at the onset but subsides after 6 months; (*b*) fibrosis is the predominant element; (*c*) infiltration is usually absent. The evolution is continuous and progressive. (2) Haemarthrosis: (*a*) synovial activity is immediate, intense, and limited to the intima; (*b*) there is no fibrosis; (*c*) infiltration of the intima is acute, consisting of polymorphonuclear cells and pigment cells. The condition is of short duration and the synovial membrane becomes normal. (3) Synovial arthritis: (*a*) synovial activity is intense and generalized; (*b*) fibrosis is a secondary element showing only degeneration of connective tissues; (*c*) the infiltration is either diffuse or in the form of nodules with predominance of plasmocytes, then monocytes, and finally polymorphonuclear neutrophils. The evolution is often prolonged and is probably under the influence of further allergic responses. *S. Maxwell.*

The Histology of Granuloma Annulare Compared with that of the Necrobiotic Nodules of Rheumatoid Arthritis. BOWERS, R. E. (1949). *Brit. J. Derm. Syph.*, **61**, 247.

The differences in histological appearance between the nodules of rheumatoid arthritis and the lesions of granuloma annulare are described with particular reference to two cases of which a description is given, one of rheumatoid arthritis and the other of granuloma annulare in which the lesions were situated deep in the skin. Although the clinical differentiation of the two conditions is usually easy, there is often a very close histological resemblance between them. The features whereby the arthritic nodule may be distinguished microscopically are described by the author as follows: (1) The degenerate areas are usually larger than those of granuloma annulare. (2) The degenerate material is usually homogeneous and the surrounding connective tissue presents an almost uninterrupted background for the endothelioid cells which it contains. (3) New vessel formation is less marked, though often present in the early stages. (4) There is a less varied cellular reaction, the elements being mainly histiocytes, often with many fibroblasts. It is postulated that the appearances in both conditions are those of reaction to collagenous degeneration. [This short paper is well illustrated.] *H. R. Vickers.*

Specificity of Differential Sheep-Cell Agglutination Test in Rheumatoid Arthritis. SULKIN, S. E., PIKE, R. M., and COGGESHALL, H. C. (1949). *Proc. Soc. exp. Biol., N.Y.*, **70**, 475.

The application of the differential sheep-cell agglutination test in rheumatoid arthritis is described, and results obtained in patients and controls are recorded. From these it is concluded that the test is of limited diagnostic value, though it may reflect to some extent the activity of the disease. *David P. Nicholson.*

Other General Articles

Arthroplasty of the Knee Joint. Late Results. SAMSON, J. E. (1949). *J. Bone Jt Surg.*, 31B, 50.

Arthroplasty of the Knee. A Follow-up Study. SPEED, J. S., and TROUT, P. C. (1949). *Ibid.*, 31B, 53.

[These two authoritative articles should be read in the original because they are so concise that they hardly lend themselves to further abstraction.] These authors must have an unparalleled experience of arthroplasty of the knee, only part of which is reflected in the present papers based on 43 cases from Samson's clinic in Montreal, and 65 from that of Speed and Trout in Memphis. In general both authorities have arrived at identical opinions and both regard arthroplasty of the knee as a reasonable operation in unilateral cases and particularly in women. The commonest condition for which successful arthroplasty was performed was gonococcal arthritis and both authors comment that the disappearance of this condition as a result of chemotherapy will render the operation less common than formerly.

Samson fashions a bony ridge on the upper end of the tibia to articulate with a corresponding groove in the lower end of the femur, but Speed and Trout use the Campbell arthroplasty in which simple broad surfaces are used. The latter emphasize the importance of retaining the extensor mechanism intact and state that the arthroplasty can easily be performed without dividing this structure. Fascia lata is usually employed though not invariably; " cellophane " has been tried by Samson, but is condemned. Speed and Trout believe that it will probably be possible to construct a vitallium mould for this arthroplasty which will hasten the process of recovery. Samson emphasizes the importance of securing co-operation from the patient and only selecting candidates who have been warned of the arduous course of exercise they will have to undergo after operation and of the pain they will suffer for many months. Many cases benefit by mobilization after injections of procaine into the neoarthrosis and most require several gentle manipulations under anaesthesia.

The bilateral operation is condemned because the

patient has rarely sufficient strength or stamina to undergo the strain necessary to mobilize the second knee.

Both authors find that 70 per cent. of those chosen for operation are satisfied with the results. It is often difficult to assess the quality of the results objectively; indeed the radiographs of knee-joints with excellent function usually show the appearances of advanced disorganization. It appears that in the majority of cases the knee is functionally stable by virtue of the muscles which control it, though on passive examination the joint may show considerable instability. Some patients may have to walk with care and think about the placing of their feet. Speed and Trout find that the function of the knee improves for 5 years after operation and becomes stationary after 10 years; this is in contrast to fascial arthroplasty of the hip, in which degeneration always occurs after 10 years.

In the discussion which followed these two papers Sir Reginald Watson-Jones was sceptical and reaffirmed his belief in the soundness of the dictum that, over a long period of time, arthrodesis gave the best functional result in any of the weight-bearing joints. Cleveland suggested that there was a danger that this operation would prove a booby-trap for the over-enthusiastic operator. *John Charnley.*

Malignant Lupus Erythematosus. BEARE, J. M. (1949). *Brit. J. Derm. Syph.*, **61**, 233.

The author suggests the replacement of the name " acute disseminated lupus erythematosus " by " malignant lupus erythematosus " and in this excellent paper he demonstrates the similarity between malignant lupus erythematosus, polyarteritis nodosa, and acute rheumatic fever. The clinical and necropsy findings in six cases of malignant lupus erythematosus are described and discussed and the relevant literature is widely reviewed. It is probable that the three conditions named above are all end-results of an anaphylactic hypersensitivity reaction, and that in lupus erythematosus the important distinguishing factor is the abnormal reaction of the patient's tissues and not the specific nature of the antigen. Indeed, it is likely that many different types of antigen may be concerned in different individuals.

[Those interested in this group of conditions are advised to consult the original paper.] *H. R. Vickers.*

***p*-Aminobenzoic Acid in Chronic Joint Disease.** (L'acido para-aminobenzoico nelle atropatie croniche.) ANDREOLA, E. (1949). *Rif. med.*, **63**, 537.

p-Aminobenzoic acid (PABA) has been used as an adjunct to other forms of therapy in patients with rheumatism. The author treated ten cases of chronic joint disease, seven diagnosed as polyarthritis of a rheumatoid type and three as " chronic arthrosis ". The patients' ages ranged from 35 to 75 years, the mean being 63 years, and suffered from a variety of associated conditions including septic foci, cardio-vascular degeneration, etc. They were treated with bed rest, removal of septic foci where practicable, morphine for a few days, and PABA, which was given by deep intramuscular injection for a varying number of days and then continued orally, or else given entirely by mouth. Total dosage varied from 60 g. to 150 g. and a variety of other drugs (iodine, belladonna, salicylate, sulphonamide, vitamins, etc.) given and physical procedures (*x*-ray therapy, radiant heat) carried out at the same time. Abscesses developed at the site of injection in three cases, and three patients had severe gastric upset. No improvement was observed in three patients, five were relieved and improved, and two were cured. [There is an obvious lack of control about this investigation.]

J. P. D. Graham.

Pathogenesis of Concurrent Eye and Joint Diseases. GODTFREDSEN, E. (1949). *Brit. J. Ophthal.*, **33**, 261.

As the aetiology and pathogenesis of many cases of iridocyclitis, scleritis, and phlyctenular conjunctivitis are still obscure, and as these diseases are frequently met with in association with diseases of joints, the author analyses the nature and frequency of eye symptoms in joint diseases in an attempt to elucidate the underlying pathology.

The medical or rheumatic joint diseases complicated by eye symptoms can be divided into two groups—acute and chronic. In the first group, rheumatic fever is complicated by conjunctivitis in 5 to 10 per cent. of cases, and by iritis in 4 to 5 per cent.; gonorrhoeal arthritis, by conjunctivitis in 10 per cent. and iritis in 5 per cent.; Reiter's disease, by conjunctivitis in 80 per cent. and iritis in 10 per cent. In the second group, primary progressive chronic polyarthritis is accompanied by iritis in 2 to 5 per cent. of cases, and by the sicca syndrome in a further 10 per cent.; Still's disease, by iritis in 20 per cent.; and ankylopoietic spondylo-arthritis, by iritis in 15 to 50 per cent.

In Denmark there are 4,000 fresh cases of rheumatic fever annually and 300 to 400 fresh cases of primary chronic polyarthritis. All other joint diseases are far less frequent, but Reiter's disease has been observed with increasing frequency. The eye symptoms in these joint diseases can be divided into three distinct groups: (1) endogenous conjunctivitis, including episcleritis and scleritis; (2) iritis and iridocyclitis; and (3) the sicca syndrome.

The pathogenesis of the joint disease is not yet fully elucidated. Rheumatic fever is probably an allergo-toxic reaction to infection with haemolytic streptococci—a hypothesis supported by an increased antistreptolysin titre in 80 per cent. of cases. The aetiology of Reiter's disease is still obscure, but a virus may be implicated. The three chronic joint diseases are presumably infective with an allergo-toxic pathogenesis. The primary infective agent giving rise to the allergo-toxic reaction in the two groups is clear only in rheumatic fever and gonorrhoeal arthritis. It is assumed that the pathogenesis of the eye signs is the same as that of the joint symptoms, being of an allergo-toxic nature. This hypothesis is supported clinically in that phlyctenular conjunctivitis and episcleritis are found in recognized allergic conditions, such as serum disease and sulphonamide and tuberculin allergy. The histopathological picture of phlyctenular conjunctivitis is the same in both groups.

It is concluded that a group of the rheumatic joint diseases which belongs to the infective type of arthritis is sometimes associated with eye symptoms, chiefly of an allergo-toxic nature. The pathogenesis is presumably the same for the eye and the joint disease. The

allergo-toxic basis is supported clinically by the resemblance in the symptomatology of the rheumatic group to that of a group, generally presumed to be allergo-toxic, affecting the eye, joints, skin, and mucous membranes. *S. J. H. Miller.*

Pain Charts. A Description of a Technique Whereby Functional Pain may be Diagnosed from Organic Pain. PALMER, H. (1949). *N.Z. med. J.*, **48**, 187.

This paper outlines a method for the recording of a patient's complaint of pain. The patient is given charts of the front and back of the body and invited to mark on them every pain which he feels. If he can distinguish different qualities of pain, the observer marks the site of each with ink of different colours. The patient may be asked which pain causes him the most concern.

Pain associated with functional nervous disorders is found as a rule to show a striking symmetry; such symmetry is almost diagnostic of a functional nervous disorder or of a functional superstructure built up round an organic lesion. Where the chart shows asymmetrical pain, there may be preoccupation with the heart and circulation, a history of operation or injury, introjection of another person's pain, a psychotic syndrome, an iatrogenic condition, an occupational neurosis, or a true psychalgia. The pain record of one patient is often reproduced very closely by another. The main sites of functional pain in each region of the body are described in detail. A number of pain charts from patients with various functional disorders are given.

[The value of this method in recording the patient's description of his pain is clear. The author's subtitle for his article, " A technique whereby functional pain may be diagnosed from organic pain ", implies, however, that description alone is sufficient for this purpose. The differential diagnosis surely rests on other aspects of the pain experience as well.] *Desmond O'Neill.*

Malignant Osteoclastoma and the Association of Malignant Osteoclastoma with Paget's Osteitis Deformans. RUSSELL, D. S. (1949). *J. Bone Jt Surg.*, **31B**, 281.

The author reviews the references in the literature to the development of metastases from solitary osteoclastoma of long bones. Histologically, she considers that the character of the stroma cells (as distinct from the osteoclastic giant cells) requires careful scrutiny in the assessment of malignancy of these tumours.

Two cases of osteoclastoma are considered which were treated by curettage, irradiation, and amputation and in which lung metastases supervened. In the first case, three successive specimens from the primary tumour, taken at intervals of months, revealed a steady progression from an apparently benign osteoclastoma to a malignant tumour, cytologically difficult to distinguish from an osteogenic sarcoma. In the second case, a subcutaneous metastasis at a distance from the primary growth showed no evidence of malignancy. (There was, however, a conspicuous formation of fine-trabecular new bone, suggesting an osteogenic capacity of the tumour cells under special circumstances.) Two different types of metastasizing process are therefore possible.

Three cases are described of histologically malignant osteoclastoma complicating Paget's disease. In these, cystic changes appeared in bone, with microscopical evidence of malignant osteoclastoma. It is suggested that of the malignant bone tumours said to complicate Paget's disease in 5 to 7 per cent. of cases, and generally described as osteogenic sarcomata, a proportion may well be malignant osteoclastomata. *Basil A. Stoll.*

The Osseous Lesions of Sarcoidosis. HOLT, J. F., and OWENS, W. I. (1949). *Radiology*, **53**, 11.

The authors briefly describe the history of sarcoidosis from the time of Boeck's original description, concerning themselves chiefly with the osseous manifestations.

The lesions occur mainly in the hands and feet; in the latter situation the lesions are said to occur with the greater frequency. The sarcoid nodule appears in the medulla of the bone, most usually in a phalanx near the joint. Histologically the lesion resembles a tubercle but has no caseous core. The giant cells are said to be larger and to contain more nuclei than those in tuberculous lesions.

Radiologically the lesions appear as a stippled translucency within the bone shaft, coalescing in places to form punched-out, rounded, or oval translucencies. When destruction of bone architecture is greater, there remains a characteristic loose network of bony trabeculae which has been likened to lacework. A feature of considerable diagnostic importance is the lack of involvement of the adjacent joint, the width of which is not reduced and the bony surfaces of which remain intact. A further diagnostic point is the absence of periosteal reaction.

Differential diagnosis, from conditions such as hyperparathyroidism, polyostoic fibrous dysplasia, gout, fungus disease, leprosy, and tuberculosis is discussed and points of difference are noted. Of the authors' 65 cases of sarcoidosis, 16 per cent. showed bone lesions; this figure agrees fairly well with the incidence of osseous sarcoid, as derived from the literature. *A. M. Rackow.*

The Effect of Microwave Diathermy on the Peripheral Circulation and on Tissue Temperature in Man. GERSTEN, J. W., WAKIM, K. G., HERRICK, J. F., and KRUSEN, F. H. (1949). *Arch. phys. Med.*, **30**, 7.

The purpose of this study was to determine the effect on the peripheral circulation and tissue temperature in the exposed area of exposure to various outputs of microwaves for different period of time. The greatest rise in temperature was found in the majority of instances in the muscles, and only very occasionally in the skin. From the foregoing it is concluded that the amount of energy absorbed by muscle after exposure to microwaves is greater than that absorbed by subcutaneous tissue or skin. This may be due to the fact that the conductivity of muscle is greater than that of fatty tissue. *M. B. Ray.*

Gonococcal Arthritis: A Study of 202 Patients Treated with Penicillin, Sulfonamides or Fever Therapy. ROBINSON, J. A., HIRSH, H. L., ZELLER, W. W., and DOWLING, H. F. (1949). *Ann. intern. Med.*, **30**, 1212.

The results of treatment in 202 cases of proved gonococcal arthritis at the Gallinger Municipal Hospital, Washington, over the past 12 years are reviewed. In this series 109 patients (53·9 per cent. were males and

93 (46·1 per cent.) females. The condition was polyarticular in 162 cases.

Fever therapy was employed in 55 cases. After use of the Kettering hypertherm 21 out of 33 patients (63·6 per cent.) were cured, whereas intravenous typhoid vaccine was found to be much less satisfactory. Various types of sulphonamides were used in 140 cases, with cure in 69·3 per cent. The type of sulphonamide used appeared to have little effect on the results of treatment, but the larger doses over a longer period used in later years seemed more effective. Penicillin therapy was used in 32 patients, of whom 71·8 per cent. were cured, but in some of the early cases of failure the dosage was probably inadequate.

In all forms of treatment used, the " acute " cases, with with symptoms for less than 30 days, responded more favourably than the " chronic " ones. The authors conclude that penicillin is the drug of choice in the treatment of gonococcal arthritis, and recommend a total of 2 to 5 million units over a period of 5 to 10 days. In the more chronic type of case, where no response is obtained to penicillin, fever therapy is sometimes more effective.

Kathleen M. Lawther.